To: Jan

Access DB# 12614

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Brian Nelson Examiner #: 78145 Date: 1/22/01

Art Unit: 1614 Phone Number 308-5127 Serial Number: 09/424,619

Mail Box and Bldg/Room Location: 2D01 CM1-2B03 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: The use of a nitroxide in a ... [illegible]

Inventors (please provide full names): James B. Mitchell et al

Earliest Priority Filing Date: 5/27/97

***For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.**

(1) 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (tempol) 2226-96-2

(2) formula I in which

R1 is O

R2, R3, R4, R5 is methyl (a C1-30 alkyl group),

n = 1

one of R6 & R7 is hydrogen & the other is hydroxyl

R8-R11 is hydrogen

****

STAFF USE ONLY

Searcher: Jan	**Type of Search**	**Vendors and cost where applicable**
Searcher Phone #: 4498	NA Sequence (#)	STN ✓
Searcher Location:	AA Sequence (#)	Dialog
Date Searcher Picked Up: 1/22	Structure (#) ✓	Questel/Orbit
Date Completed: 1/30	Bibliographic ✓	Dr.Link
Searcher Prep & Review Time:	Litigation	Lexis/Nexis
Clerical Prep Time: 20	Fulltext	Sequence Systems
Online Time: [illegible]	Patent Family	WWW/Internet
	Other	Other (specify)

PTO-1590 (1-2000)

L13 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2001 ACS
CN 1-Piperidinyloxy, 4-hydroxy-2,2,6,6-tetramethyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Piperidinooxy, 4-hydroxy-2,2,6,6-tetramethyl- (7CI, 8CI)
OTHER NAMES:
CN 1-Oxyl-2,2,6,6-tetramethyl-4-hydroxypiperidine
CN 1-Oxyl-2,2,6,6-tetramethyl-4-piperidinol
CN 2,2,6,6-Tetramethyl-1-oxy-4-hydroxypiperidine
CN 2,2,6,6-Tetramethyl-4-hydroxy-1-piperidinyloxy radical
CN 2,2,6,6-Tetramethyl-4-hydroxylpiperidine-1-oxyl
CN 2,2,6,6-Tetramethyl-4-hydroxypiperidin-1-oxyl
CN 2,2,6,6-Tetramethyl-4-hydroxypiperidine 1-oxide radical
CN 2,2,6,6-Tetramethyl-4-hydroxypiperidine oxide
CN 2,2,6,6-Tetramethyl-4-hydroxypiperidine-1-hydroxyl
CN 2,2,6,6-Tetramethyl-4-hydroxypiperidine-1-oxyl
CN 2,2,6,6-Tetramethyl-4-hydroxypiperidine-1-oxyl radical
CN 2,2,6,6-Tetramethyl-4-hydroxypiperidinooxy
CN 2,2,6,6-Tetramethyl-4-hydroxypiperidinooxy radical
CN 2,2,6,6-Tetramethyl-4-hydroxypiperidinyl-1-oxy
CN 2,2,6,6-Tetramethyl-4-hydroxypiperidinyl-1-oxyl
CN 2,2,6,6-Tetramethyl-4-hydroxypiperidinyloxy radical
CN 2,2,6,6-Tetramethyl-4-hydroxypiperidinyloxyl radical
CN 2,2,6,6-Tetramethyl-4-hydroxypiperidyl 1-oxyl
CN 2,2,6,6-Tetramethyl-4-oxypiperidine-1-oxyl
CN 2,2,6,6-Tetramethyl-4-piperidinol 1-oxide
CN 2,2,6,6-Tetramethyl-4-piperidinol 1-oxyl
CN 2,2,6,6-Tetramethyl-4-piperidinol N-oxyl
CN 2,2,6,6-Tetramethyl-4-piperidinol nitroxide
CN 2,2,6,6-Tetramethyl-4-piperidinol-1-oxy
CN 2,2,6,6-Tetramethyl-4-piperidinol-1-oxyl radical
CN 2,2,6,6-Tetramethylpiperidine-4-hydroxy-1-oxyl
CN 2,2,6,6-Tetramethylpiperidine-N-oxyl-4-ol
CN 2,2,6,6-Tetramethylpiperidinol-4-oxyl-1
CN 4-Hydroxy-1-oxyl-2,2,6,6-tetramethylpiperidine
CN 4-Hydroxy-2,2,6,6-tetramethyl-1-piperidinoxy
CN 4-Hydroxy-2,2,6,6-tetramethyl-1-piperidinoxyl
CN 4-Hydroxy-2,2,6,6-tetramethyl-1-piperidinyloxy
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidine 1-oxide radical
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidine N-oxide
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidine-N-oxy
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidino-1-oxyl
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidinooxy
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidinooxy radical
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidinoxy
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidinoxyl
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidinyl-1-oxyl
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidinyl-N-oxy
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidinyl-N-oxyl
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidyl-1-oxyl
CN 4-hydroxy-TEMPO
CN 4-Oxypiperidol
CN 4H-Tempo
CN HOTEMPO
CN HTEMPO
CN HyTEMPO
CN Nitroxyl 2
CN NR I
CN Tanol
CN Tempo OH
CN Tempol
CN Tetramethyl-2,2,6,6-aza-1-cyclohexanol-4-oxide-1

TEMPOL

741

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=> d his

     (FILE 'HOME' ENTERED AT 12:12:38 ON 30 JAN 2001)
               SET COST OFF

     FILE 'HCAPLUS' ENTERED AT 12:12:51 ON 30 JAN 2001
               E WO9853835/PN
L1               1 S E3
               E MITCHELL J/AU
L2             379 S E3,E5-E8
               E MITCHELL JAMES/AU
L3             174 S E3,E6-E8
L4               3 S E80
               E RUSSO A/AU
L5             256 S E3-E17
L6              83 S E43
               E CHERUKURI M/AU
L7               4 S E4-E6
L8               2 S E18
               E DELUCA A/AU
L9               6 S E3,E4,E11
L10             13 S E13,E14
               E DE LUCA A/AU
L11             81 S E3,E4,E9,E11
               E LUCA A/AU
L12              9 S E3,E12

     FILE 'REGISTRY' ENTERED AT 12:16:25 ON 30 JAN 2001
L13              1 S 2226-96-2
L14             29 S 2226-96-2/CRN

     FILE 'HCAOLD' ENTERED AT 12:17:49 ON 30 JAN 2001
L15             25 S L13
L16              1 S L14
L17              0 S TEMPOL OR TEMPO OH OR HTEMPO OR HYTEMPO OR HOTEMPO OR TANOL O
L18              2 S L15 AND ?TUMOR?

     FILE 'HCAPLUS' ENTERED AT 12:18:52 ON 30 JAN 2001
L19           1706 S L13 OR L14
L20            694 S TEMPOL OR TEMPO OH OR HTEMPO OR HYTEMPO OR HOTEMPO OR TANOL O
L21              3 S HYDROXY(4W)(TETRAMETHYL OR TETRA METHYL)(1W)(PIPERIDINOOXY)
L22            163 S (TETRAMETHYL OR TETRA METHYL)(S)(HYDROXYPIPERIDIN? OR HYDROXY
L23            319 S (TETRAMETHYL OR TETRA METHYL)(S)(HYDROXYPIPERIDIN? OR HYDROXY
L24            345 S (TETRAMETHYLPIPERIDIN? OR TETRA METHYL PIPERIDIN?)(S)HYDROXY
L25             62 S (TETRAMETHYL OR TETRA METHYL)(S)PIPERIDINOL(S)OXY#
L26             22 S (TETRAMETHYL OR TETRA METHYL)(S)PIPERIDINOL(S)NITROXIDE
L27             66 S HYDROXY(S)(TETRAMETHYL OR TETRA METHYL)(S)PIPERIDIN?(S)OXY#
L28            141 S HYDROXY(S)(TETRAMETHYL OR TETRA METHYL)(S)(PIPERIDINOXY OR PI
L29             32 S HYDROXY(S)(TETRAMETHYL OR TETRA METHYL)(S)PIPERIDINOXY?
L30             22 S HYDROXY(S)TETRAMETHYLPIPERIDINOXY?
L31            702 S L19 NOT L20-L30
L32           2158 S L19-L31
L33             33 S L32 AND L2-L12
L34              1 S L1 AND L33
               E NITROXIDE/CT
               E E5+ALL/CT
L35           5025 S E2+NT/CT
L36             37 S L2-L12 AND L35
L37             40 S L33,L36
L38              1 S L37 AND L1
L39             39 S L37 NOT L38
L40           4495 S L32,L35 AND (PD<=19970527 OR PRD<=19970527 OR AD<=19970527 OR
L41              1 S P53 AND L40
               E TUMOR SUPPRES/CT
               E E7+ALL/CT
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L42        1166 S E1+NT
                E E2+ALL/CT
L43        1771 S E3 (L) TUMOR (L) SUPPRES?
                E GENE/CW
L44        3434 S E3,E12 (L) TUMOR (L) SUPPRES?
L45           1 S L40 AND L42-L44
L46           3 S E3,E12 AND L40
L47          27 S L39 AND L40
L48          12 S L39 NOT L47
L49           2 S L48 AND ?TUMOR?
L50         128 S L40 AND (?NEOPLAS? OR ?TUMOR? OR ?TUMOUR? OR ?CANCER? OR ?CAR
L51          33 S L40 AND (?MUTANT? OR ?MUTAT?)
L52         156 S L50-L51
                E NEOPLAS/CT
L53          24 S E6+NT/CT AND L40
                E TUMOR/CT
L54           0 S E3+NT/CT AND L40
L55           4 S E125+NT/CT AND L40
L56           0 S E124+NT/CT AND L40
                E TUMOR INHIBITOR/CT
                E E4+ALL/CT
L57          17 S E2+NT/CT AND L40
                E NEOPLASM INHIBITOR/CT
L58          45 S E10+NT/CT AND L40
                E E10+ALL/CT
L59         158 S L52,L53,L55,L57,L58
L60          23 S ?MUTAGEN? AND L40
L61         164 S L59,L60
L62          66 S L19 AND L61
L63           2 S L62 AND 4/SC AND ANTIMUTAGEN?/TI
L64           1 S L63 NOT TA98/TI
L65           3 S L62 AND 8/SC AND (RADIOPROTECT? OR RADIOSENSIT?)/TI
L66           1 S L62 AND 62/SC AND PHOTOAG?/TI
L67           9 S L62 AND (1 OR 63)/SC AND (SCAVENG? OR LEUKEMIA OR NEUROBLASTO
L68           7 S L67 NOT (TEPA OR PODOPHYL?)/TI
L69          98 S L61 NOT L62-L68
L70           1 S L69 AND 8/SC AND (RADIATION ONCOLOGY)/TI
L71           1 S L69 AND 14/SC AND NEW DIRECTION/TI
L72           7 S L69 AND 1/SC AND (TMPO OR PRODRUG OR IRRADIATION OR TOXICITY
L73           5 S L72 NOT (TRIAMIDE OR HEPATOCYTE)/TI
L74          19 S L64-L66,L68,L70,L71,L73
L75          23 S L41,L45,L46,L49,L74
L76          27 S L39 AND L40
L77          44 S L75,L76
L78          10 S L39 NOT L77
L79          54 S L77,L78
                E TRANSITION METAL/CT
                E TRANSITION METALS/CT
                E E3+ALL/CT
L80          28 S L40 AND E5,E10,E26,E27,E33,E44,E64,E65,E66,E102-E105,E182,E18
L81           2 S L40 AND E310+NT/CT
L82           5 S L40 AND E311
L83          34 S L40 AND (TRANSITION(S)METAL?)/CW
L84          10 S L40 AND LANTHANID?
                E LANTHANIDE/CT
                E E16+ALL/CT
L85           1 S L40 AND E2+NT/CT
L86           0 S L40 AND E3+NT/CT
                E LANTHANIDES/CT
                E E3+ALL/CT
L87          29 S E2+NT/CT AND L40
                E E2+ALL/CT
L88          11 S L40 AND E7,E84
L89          61 S L80-L88
L90          13 S L89 AND (1 OR 8 OR 62 OR 63)/SC,SX
L91           2 S L89 AND L61
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L92            1 S L89 AND CELL DAMAGE
L93           56 S L79,L91,L92
                 SEL HIT RN

     FILE 'REGISTRY' ENTERED AT 13:27:11 ON 30 JAN 2001
L94            5 S E1-E5

     FILE 'HCAPLUS' ENTERED AT 13:27:43 ON 30 JAN 2001
L95         1689 S L13
L96           36 S L95 AND L93
L97           20 S L93 NOT L96

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FILE 'REGISTRY' ENTERED AT 13:28:22 ON 30 JAN 2001
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2001 American Chemical Society (ACS)

STRUCTURE FILE UPDATES:   29 JAN 2001  HIGHEST RN 318233-39-5
DICTIONARY FILE UPDATES:  29 JAN 2001  HIGHEST RN 318233-39-5

TSCA INFORMATION NOW CURRENT THROUGH July 8, 2000

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Structure search limits have been increased.  See HELP SLIMIT
for details.

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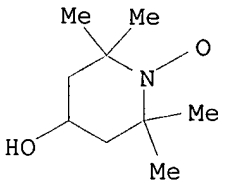
L13  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2001 ACS
RN   2226-96-2  REGISTRY
CN   1-Piperidinyloxy, 4-hydroxy-2,2,6,6-tetramethyl- (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   1-Oxyl-2,2,6,6-tetramethyl-4-hydroxypiperidine
CN   1-Oxyl-2,2,6,6-tetramethyl-4-piperidinol
CN   2,2,6,6-Tetramethyl-1-oxy-4-hydroxypiperidine
CN   2,2,6,6-Tetramethyl-4-hydroxy-1-piperidinyloxy radical
CN   2,2,6,6-Tetramethyl-4-hydroxylpiperidine-1-oxyl
CN   2,2,6,6-Tetramethyl-4-hydroxypiperidin-1-oxyl
CN   2,2,6,6-Tetramethyl-4-hydroxypiperidine 1-oxide radical
CN   2,2,6,6-Tetramethyl-4-hydroxypiperidine oxide
CN   2,2,6,6-Tetramethyl-4-hydroxypiperidine-1-hydroxyl
CN   2,2,6,6-Tetramethyl-4-hydroxypiperidine-1-oxyl
CN   2,2,6,6-Tetramethyl-4-hydroxypiperidine-1-oxyl radical
CN   2,2,6,6-Tetramethyl-4-hydroxypiperidinooxy
CN   2,2,6,6-Tetramethyl-4-hydroxypiperidinooxy radical
CN   2,2,6,6-Tetramethyl-4-hydroxypiperidinyl-1-oxy
CN   2,2,6,6-Tetramethyl-4-hydroxypiperidinyl-1-oxyl
CN   2,2,6,6-Tetramethyl-4-hydroxypiperidinyloxy radical
CN   2,2,6,6-Tetramethyl-4-hydroxypiperidinyloxyl radical
CN   2,2,6,6-Tetramethyl-4-hydroxypiperidyl 1-oxyl
CN   2,2,6,6-Tetramethyl-4-oxypiperidine-1-oxyl
CN   2,2,6,6-Tetramethyl-4-piperidinol 1-oxide
CN   2,2,6,6-Tetramethyl-4-piperidinol 1-oxyl
CN   2,2,6,6-Tetramethyl-4-piperidinol N-oxyl
CN   2,2,6,6-Tetramethyl-4-piperidinol nitroxide
CN   2,2,6,6-Tetramethyl-4-piperidinol-1-oxy
CN   2,2,6,6-Tetramethyl-4-piperidinol-1-oxyl radical
CN   2,2,6,6-Tetramethylpiperidine-4-hydroxy-1-oxyl
CN   2,2,6,6-Tetramethylpiperidine-N-oxyl-4-ol
CN   2,2,6,6-Tetramethylpiperidinol-4-oxyl-1
CN   4-Hydroxy-1-oxyl-2,2,6,6-tetramethylpiperidine
```

CN 4-Hydroxy-2,2,6,6-tetramethyl-1-piperidinoxy
CN 4-Hydroxy-2,2,6,6-tetramethyl-1-piperidinoxyl
CN 4-Hydroxy-2,2,6,6-tetramethyl-1-piperidinyloxy
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidine 1-oxide radical
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidine N-oxide
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidine-N-oxy
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidino-1-oxyl
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidinooxy
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidinooxy radical
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidinoxy
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidinoxyl
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidinyl-1-oxyl
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidinyl-N-oxy
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidinyl-N-oxyl
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidyl-1-oxyl
CN 4-hydroxy-TEMPO
CN 4-Oxypiperidol
CN 4H-Tempo
CN HOTEMPO
ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for DISPLAY
DR 13075-58-6, 3174-32-1, 105269-77-0, 119227-61-1, 68541-96-8, 70939-25-2, 38854-37-4
MF C9 H18 N O2
CI COM
LC STN Files: ADISINSIGHT, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DETHERM*, DRUGU, EMBASE, GMELIN*, IFICDB, IFIPAT, IFIUDB, IMSDIRECTORY, MEDLINE, MSDS-OHS, NIOSHTIC, PIRA, RTECS*, TOXLINE, TOXLIT, ULIDAT, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, NDSL**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)



1680 REFERENCES IN FILE CA (1967 TO DATE)
44 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1682 REFERENCES IN FILE CAPLUS (1967 TO DATE)
24 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 134:73247

REFERENCE 2: 134:73062

REFERENCE 3: 134:72037

REFERENCE 4: 134:72036

REFERENCE 5: 134:72025

REFERENCE 6: 134:71471

REFERENCE 7: 134:71263

REFERENCE 8: 134:65958

REFERENCE 9: 134:54773

REFERENCE 10: 134:42567

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L98 4 L94 NOT L13

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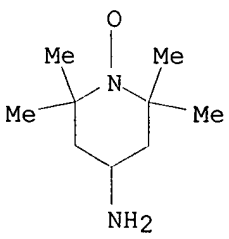
L98 ANSWER 1 OF 4 REGISTRY COPYRIGHT 2001 ACS
RN **14691-88-4** REGISTRY
CN 1-Piperidinyloxy, 4-amino-2,2,6,6-tetramethyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Piperidinooxy, 4-amino-2,2,6,6-tetramethyl- (8CI)
OTHER NAMES:
CN (2,2,6,6-Tetramethyl-1-oxy-4-piperidinyl)amine
CN 2,2,6,6-Tetramethyl-1-oxy-4-aminopiperidine
CN 2,2,6,6-Tetramethyl-4-amino-1-piperidinyloxy
CN 2,2,6,6-Tetramethyl-4-aminopiperidine N-oxide
CN 2,2,6,6-Tetramethyl-4-aminopiperidine-1-oxyl
CN 4-Amino-1-oxyl-2,2,6,6-tetramethylpiperidine
CN 4-Amino-2,2,6,6-tetramethyl-1-piperidinyloxy
CN 4-Amino-2,2,6,6-tetramethyl-1-piperidinyloxyl
CN 4-Amino-2,2,6,6-tetramethylpiperidin-1-oxyl
CN 4-Amino-2,2,6,6-tetramethylpiperidine-1-oxy
CN 4-Amino-2,2,6,6-tetramethylpiperidine-1-oxyl
CN 4-Amino-2,2,6,6-tetramethylpiperidine-N-oxyl
CN 4-Amino-2,2,6,6-tetramethylpiperidino-1-oxy
CN 4-Amino-2,2,6,6-tetramethylpiperidino-1-oxyl
CN 4-Amino-2,2,6,6-tetramethylpiperidinooxyl
CN 4-Amino-2,2,6,6-tetramethylpiperidinyl-N-oxy
CN 4-Amino-2,2,6,6-tetramethylpiperidinyloxy
CN 4-Aminotempo
CN 6-Tempamine
CN Tempamine
CN Tempo-amine
DR 125342-82-7, 78774-22-8, 26947-98-8
MF C9 H19 N2 O
CI COM
LC STN Files: AGRICOLA, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CHEMCATS, CHEMINFORMRX, CHEMLIST, CSCHEM, DDFU, DRUGU, EMBASE, GMELIN*, IFICDB, IFIPAT, IFIUDB, MEDLINE, SYNTHLINE, TOXLINE, TOXLIT, ULIDAT, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, NDSL**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)



585 REFERENCES IN FILE CA (1967 TO DATE)
42 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
585 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:73247

REFERENCE 2: 134:71471

REFERENCE 3: 134:57938

REFERENCE 4: 134:18439

REFERENCE 5: 133:363759

REFERENCE 6: 133:322330

REFERENCE 7: 133:311086

REFERENCE 8: 133:284079

REFERENCE 9: 133:209532

REFERENCE 10: 133:185450

L98 ANSWER 2 OF 4 REGISTRY COPYRIGHT 2001 ACS
RN **7440-54-2** REGISTRY
CN Gadolinium (8CI, 9CI) (CA INDEX NAME)
DR 87677-94-9, 110123-54-1
MF Gd
CI COM
LC STN Files: AGRICOLA, AIDSLINE, ANABSTR, APILIT, APILIT2, APIPAT, APIPAT2, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NIOSHTIC, PIRA, PROMT, RTECS*, TOXLINE, TOXLIT, TULSA, ULIDAT, USPATFULL, VTB
(*File contains numerically searchable property data)
Other Sources: EINECS**, NDSL**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

Gd

19120 REFERENCES IN FILE CA (1967 TO DATE)
2439 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
19144 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:80115

REFERENCE 2: 134:79914

REFERENCE 3: 134:79497

REFERENCE 4: 134:78036

REFERENCE 5: 134:77826

REFERENCE 6: 134:77802

REFERENCE 7: 134:77737

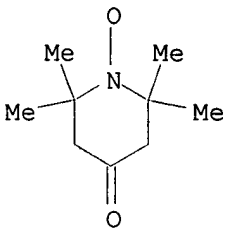
REFERENCE 8: 134:77054

REFERENCE 9: 134:75895

REFERENCE 10: 134:74815

L98 ANSWER 3 OF 4 REGISTRY COPYRIGHT 2001 ACS
RN **2896-70-0** REGISTRY

CN 1-Piperidinyloxy, 2,2,6,6-tetramethyl-4-oxo- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Piperidinooxy, 2,2,6,6-tetramethyl-4-oxo- (8CI)
OTHER NAMES:
CN 1-Oxyl-2,2,6,6-tetramethyl-4-piperidone
CN 1-Oxyl-2,2,6,6-tetramethylpiperidin-4-one
CN 2,2',6,6'-Tetramethyl-4-oxopiperidine-1-oxyl
CN 2,2,6,6-Tetramethyl-4-oxo-1-piperidinooxy
CN 2,2,6,6-Tetramethyl-4-oxo-1-piperidinyloxy
CN 2,2,6,6-Tetramethyl-4-oxo-1-piperidinyloxyl
CN 2,2,6,6-Tetramethyl-4-oxo-piperydin-1-oxyl
CN 2,2,6,6-Tetramethyl-4-oxopiperidin-1-oxyl
CN 2,2,6,6-Tetramethyl-4-oxopiperidin-1-oxyl radical
CN 2,2,6,6-Tetramethyl-4-oxopiperidine-1-oxyl
CN 2,2,6,6-Tetramethyl-4-oxopiperidine-1-oxyl radical
CN 2,2,6,6-Tetramethyl-4-oxopiperidinooxy
CN 2,2,6,6-Tetramethyl-4-oxypiperidin-1-oxyl
CN 2,2,6,6-Tetramethyl-4-piperidinone-1-oxyl
CN 2,2,6,6-Tetramethyl-4-piperidon-1-oxyl
CN 2,2,6,6-Tetramethyl-4-piperidone 1-nitroxide
CN 2,2,6,6-Tetramethyl-4-piperidone nitroxide
CN 2,2,6,6-Tetramethyl-4-piperidone-N-oxide
CN 2,2,6,6-Tetramethyl-4-piperidone-N-oxy
CN 2,2,6,6-Tetramethyl-4-piperidone-N-oxyl
CN 2,2,6,6-Tetramethylpiperid-4-one-1-oxyl
CN 2,2,6,6-Tetramethylpiperidone-1-oxyl
CN 4-Oxo-2,2,6,6-tetramethyl-1-piperidinoxyl
CN 4-Oxo-2,2,6,6-tetramethylpiperidine-1-oxyl
CN 4-Oxo-2,2,6,6-tetramethylpiperidine-N-oxyl
CN 4-Oxo-2,2,6,6-tetramethylpiperidino-1-oxy
CN 4-Oxo-2,2,6,6-tetramethylpiperidino-N-oxyl
CN 4-Oxo-2,2,6,6-tetramethylpiperidinooxy
CN 4-Oxo-2,2,6,6-tetramethylpiperidinooxyl
CN 4-Oxo-2,2,6,6-tetramethylpiperidinoxyl
CN 4-Oxo-2,2,6,6-tetramethylpiperidinyl-1-oxy
CN 4-Oxo-2,2,6,6-tetramethylpiperidinyloxy
CN 4-Oxo-TEMPO
CN OTEMPO
CN TAN
CN TAN (radical)
CN TANO
CN Tanone
CN Tanone radical
CN Tempone
CN Tetramethyl-2,2,6,6-aza-1-cyclohexanone-4-oxide-1
CN Triacetoneamine N-oxyl
CN Triacetoneamine nitroxide
DR 70939-26-3, 26841-66-7
MF C9 H16 N O2
CI COM
LC STN Files: AGRICOLA, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CSCHEM, EMBASE, GMELIN*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, NIOSHTIC, RTECS*, SPECINFO, TOXLINE, TOXLIT, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, NDSL**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)



960 REFERENCES IN FILE CA (1967 TO DATE)
13 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
963 REFERENCES IN FILE CAPLUS (1967 TO DATE)
27 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 134:73247

REFERENCE 2: 134:72036

REFERENCE 3: 133:343664

REFERENCE 4: 133:322570

REFERENCE 5: 133:322330

REFERENCE 6: 133:303333

REFERENCE 7: 133:281495

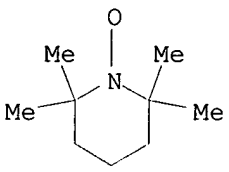
REFERENCE 8: 133:252852

REFERENCE 9: 133:252363

REFERENCE 10: 133:238802

L98 ANSWER 4 OF 4 REGISTRY COPYRIGHT 2001 ACS
RN **2564-83-2** REGISTRY
CN 1-Piperidinyloxy, 2,2,6,6-tetramethyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Piperidinooxy, 2,2,6,6-tetramethyl- (7CI, 8CI)
OTHER NAMES:
CN 1,1,5,5-Tetramethylpentamethylene nitroxide
CN 1-Oxyl-2,2,6,6-tetramethylpiperidine
CN 2,2',6,6'-Tetramethylpiperidinooxy radical
CN 2,2,6,6-Tetramethyl-1-oxylpiperidine
CN 2,2,6,6-Tetramethyl-1-piperadoxyl
CN 2,2,6,6-Tetramethyl-1-piperidinoxyl
CN 2,2,6,6-Tetramethyl-1-piperidinyloxy
CN 2,2,6,6-Tetramethyl-1-piperidyloxy
CN 2,2,6,6-Tetramethylpiperidin-1-oxy
CN 2,2,6,6-Tetramethylpiperidin-1-oxyl radical
CN 2,2,6,6-Tetramethylpiperidin-N-oxyl
CN 2,2,6,6-Tetramethylpiperidine N-oxide radical
CN 2,2,6,6-Tetramethylpiperidine N-oxy
CN 2,2,6,6-Tetramethylpiperidine N-oxyl
CN 2,2,6,6-Tetramethylpiperidine N-oxyl radical
CN 2,2,6,6-Tetramethylpiperidine nitroxide
CN 2,2,6,6-Tetramethylpiperidine nitroxide radical
CN 2,2,6,6-Tetramethylpiperidine-1-oxyl
CN 2,2,6,6-Tetramethylpiperidino-1-oxy
CN 2,2,6,6-Tetramethylpiperidinooxy
CN 2,2,6,6-Tetramethylpiperidinooxy radical
CN 2,2,6,6-Tetramethylpiperidinooxyl
CN 2,2,6,6-Tetramethylpiperidinoxyl radical
CN 2,2,6,6-Tetramethylpiperidinyl 1-oxide

CN 2,2,6,6-Tetramethylpiperidinyl-1-oxyl
CN 2,2,6,6-Tetramethylpiperidinyl-N-oxy
CN 2,2,6,6-Tetramethylpiperidinyloxy
CN 2,2,6,6-Tetramethylpiperidoxyl
CN HO 6
CN Tanan
CN Tanane
CN Tempo
DR 126517-51-9, 54637-06-8, 125012-91-1, 64104-42-3, 25657-03-8, 26933-82-4
MF C9 H18 N O
CI COM
LC STN Files: AGRICOLA, AIDSLINE, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU, GMELIN*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, NIOSHTIC, PROMT, RTECS*, TOXLINE, TOXLIT, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)



1891 REFERENCES IN FILE CA (1967 TO DATE)
73 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1894 REFERENCES IN FILE CAPLUS (1967 TO DATE)
23 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 134:73247

REFERENCE 2: 134:72071

REFERENCE 3: 134:72037

REFERENCE 4: 134:72036

REFERENCE 5: 134:72025

REFERENCE 6: 134:71837

REFERENCE 7: 134:57072

REFERENCE 8: 134:42334

REFERENCE 9: 134:29850

REFERENCE 10: 134:29814

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FILE LAST UPDATED: 29 Jan 2001 (20010129/ED)

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L96 ANSWER 1 OF 36 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:285502 HCAPLUS
DN 133:70812
TI Evaluation of the hydroxylamine **tempol**-H as an in vivo radioprotector
AU Hahn, S. M.; Krishna, M. C.; **DeLuca, A. M.**; Coffin, D.; **Mitchell, J. B.**
CS Department of Radiation Oncology, Hospital of the University of Pennsylvania, Philadelphia, PA, USA
SO Free Radical Biol. Med. (2000), 28(6), 953-958
CODEN: FRBMEH; ISSN: 0891-5849
PB Elsevier Science Inc.
DT Journal
LA English
AB Nitroxides are stable free radical compds. that protect against the toxicity of reactive oxygen species in vitro and in vivo. **Tempol** (Aldrich, Milwaukee, WI, USA) is a cell-permeable hydrophilic nitroxide and has been shown to be an in vitro and in vivo radioprotector. The limitations of **Tempol** as a systemic radioprotector are that it causes substantial redns. in arterial blood pressure when administered i.v. and is assocd. with seizure activity. Furthermore, **Tempol** is rapidly reduced to its hydroxylamine form, **Tempol**-H, which limits the period of time the active form of the nitroxide is available for radioprotection. Based on initial pharmacol. and blood pressure expts. performed in mice, we hypothesized that the systemic administration of **Tempol**-H in vivo would lead to an equilibration between **Tempol** and **Tempol**-H that would limit the toxicity of the nitroxide and provide in vivo radioprotection. **Tempol**-H was administered in increasing doses via an i.p. route to C3H mice. The maximally tolerated dose was found to be 325 mg/kg. The whole-blood pharmacol. of **Tempol**-H was investigated with ESR spectroscopy. These studies demonstrated the appearance of **Tempol** in whole blood immediately after i.p. injection, suggesting that rapid oxidn. of **Tempol**-H to **Tempol** takes place in vivo. Although the peak concn. of **Tempol** in whole blood after administration of **Tempol**-H did not reach the same levels as those obsd. when **Tempol** is administered, the whole-blood levels of **Tempol** were similar by 10 min after injection. **Tempol**-H provided protection against the lethality of whole-body radiation in C3H mice at 30 d with a dose modification factor of 1.3, which is similar to the results obtained with **Tempol**. Hemodynamic measurements in C3H mice after i.v. injection showed that **Tempol**-H produced little effect on blood pressure or pulse compared with **Tempol**. **Tempol**-H is a systemic in vivo radioprotector of C3H mice and is assocd. with less hemodynamic toxicity than **Tempol**.
IT **2226-96-2, Tempol**

RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(evaluation of **Tempol**-H as an in vivo radioprotector)
RE.CNT 19
RE
(1) Belkin, S; Arch Biochem Biophys 1987, V256, P232 HCAPLUS
(2) Chateauneuf, J; J Organ Chem 1988, V53, P1629 HCAPLUS
(5) Goffman, T; Int J Radiat Oncol Biol Phys 1992, V22, P803 HCAPLUS
(6) Hahn, S; Can J Physiol Pharmacol 1995, V73, P399 HCAPLUS
(7) Hahn, S; Cancer Res 1992, V52, P1750 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L96 ANSWER 2 OF 36 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:264668 HCAPLUS
DN 133:159857
TI Neuroprotection by the stable nitroxide **Tempol** during reperfusion in a rat model of transient focal ischemia
AU Rak, Ramin; Chao, Daniel L.; Pluta, Ryszard M.; **Mitchell, James B.**; Oldfield, Edward H.; Watson, Joe C.
CS Surgical Neurology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA
SO J. Neurosurg. (2000), 92(4), 646-651
CODEN: JONSAC; ISSN: 0022-3085
PB American Association of Neurological Surgeons
DT Journal
LA English
AB Object. The use of thrombolytic agents in the treatment of stroke has yielded surprisingly modest success, possibly because of reperfusion injury mediated by reactive oxygen species (ROS). Therefore, scavenging ROS may be of therapeutic value in the treatment of stroke. Nitroxides are low-wt. superoxide dismutase mimics, which allows them to act as cell-permeable antioxidants. In this study the nitroxide 4-**hydroxy**-2,2,6,6,-**tetramethylpiperidine**-1-**oxyl** (**Tempol**) is investigated to det. its ability to reduce reperfusion injury. Methods. Male Sprague-Dawley rats weighing between 280 g and 350 g underwent middle cerebral artery occlusion with an intraluminal suture for 60 min. Regional cerebral blood flow, blood pressure, cerebral temp., and rectal temp. were monitored during the procedure. After reperfusion, the animals were randomized to groups receiving blinded i.v. administration of either **Tempol** (10 mg/kg; eight animals) or vehicle (eight animals) over the first 20 min of reperfusion (Study I). In a second study to det. dose dependency, animals were randomized to groups receiving **Tempol** (20 mg/kg; eight animals), low-dose **Tempol** (5 mg/kg; eight animals), or vehicle (eight animals; Study II). The rats were killed after 4 h of reperfusion, and brain sections were stained with 2,3,5 triphenyltetrazolium chloride. Infarct vols. were measured using digital imaging. Animals receiving **Tempol** had significantly reduced infarct vols. at doses of 20 mg/kg and 10 mg/kg compared with controls (49.01.+-.18.22% redn. [p = 0.003] and 47.47.+-.34.57 [p = 0.02], resp.). No significant differences in the physiol. variables measured were obsd. between groups. Conclusions. **Tempol** provides significant neuroprotection after reperfusion in a rat model of transient focal ischemia. These results support the importance of ROS in reperfusion injury and encourage further study of this mol. as a therapeutic agent following thrombolysis.
IT **2226-96-2, Tempol**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neuroprotection by the stable nitroxide **Tempol** during reperfusion in a rat model of transient focal ischemia)
RE.CNT 24
RE
(1) Beit-Yannai, E; Brain Res 1996, V717, P22 HCAPLUS
(3) Cao, X; Brain Res 1994, V644, P267 HCAPLUS
(4) Floyd, R; FASEB J 1990, V4, P2587 HCAPLUS
(6) Globus, M; J Neurochem 1995, V65, P1250 HCAPLUS

(7) Hahn, S; Cancer Res 1992, V52, P1750 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L96 ANSWER 3 OF 36 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:569444 HCAPLUS
DN 131:317718
TI Hemodynamic effect of the nitroxide superoxide dismutase mimics
AU Hahn, S. M.; Sullivan, F. J.; **DeLuca, A. M.**; Bacher, J. D.; Liebmann, J.; Krishna, M. C.; Coffin, D.; **Mitchell, J. B.**
CS National Center for Research Resources, Veterinary Resources Program, National Institutes of Health, Bethesda, MD, USA
SO Free Radical Biol. Med. (1999), 27(5/6), 529-535
CODEN: FRBMEH; ISSN: 0891-5849
PB Elsevier Science Inc.
DT Journal
LA English
AB Reactive oxygen species play crit. roles in a no. of physiol. and pathol. processes. Nitroxides are stable free radical compds. that possess superoxide dismutase (SOD) mimetic activity and have been shown to protect against the toxicity of reactive oxygen species in vitro and in vivo. **Tempol**, a cell-permeable hydrophilic nitroxide, protects against oxidative stress and also is an in vitro and in vivo radioprotector. In the course of evaluating the pharmacol. and toxicity of the nitroxides, **Tempol** and another nitroxide, 3-carbamoyl-PROXYL (3-CP), were administered i.v. in various concns. to miniature swine. **Tempol** caused dose-related hypotension accompanied by reflex tachycardia and increased skin temp. Invasive hemodynamic monitoring with Swan Ganz catheterization (SGC) confirmed the potent vasodilative effect of **Tempol**. However, 3-CP had no effect on porcine blood pressure. The hemodynamic effects of **Tempol** and 3-CP are discussed in the context of differential catalytic rate consts. for superoxide dismutation that may impact systemic nitric oxide (NO) levels and lead to vasodilation. These findings are consistent with a role for the superoxide ion in the modulation of blood pressure and have potential implications for the systemic use of nitroxides.
IT **2226-96-2**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(hemodynamic effect of nitroxide superoxide dismutase mimics)
RE.CNT 27
RE
(1) Bouloumie, A; Hypertension 1997, V30, P934 HCAPLUS
(2) Hahn, S; Can J Physiol Pharmacol 1995, V73, P399 HCAPLUS
(3) Hahn, S; Cancer Res 1992, V52, P1750 HCAPLUS
(4) Hahn, S; Free Radic Biol Med 1997, V22, P1211 HCAPLUS
(6) Hahn, S; Radiat Res 1992, V132, P87 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L96 ANSWER 4 OF 36 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:5882 HCAPLUS
DN 130:206760
TI In vivo radioprotection and effects on blood pressure of the stable free radical nitroxides
AU Hahn, Stephen M.; **DeLuca, Anne Marie**; Coffin, Debbie; Krishna, C. Murali; **Mitchell, James B.**
CS Department of Radiation Oncology, University of Pennsylvania, Philadelphia, PA, USA
SO Int. J. Radiat. Oncol., Biol., Phys. (1998), 42(4), 839-842
CODEN: IOBPD3; ISSN: 0360-3016
PB Elsevier Science Inc.
DT Journal
LA English
AB The purpose of this study was to screen several water sol. nitroxides for in vivo radioprotection, to evaluate their pharmacol., and to measure the effect of nitroxides on systemic blood pressure as a means of exploring

the mechanism of in vivo radioprotection. A no. of water sol. nitroxides were screened for in vivo radioprotection in C3H mice at a single radiation dose. Selected nitroxides were administered by the i.p. route 10 min prior to a whole body radiation dose of 9 Gy. ESR spectroscopy (EPR) was used to measure whole blood levels of nitroxides. The nitroxides were evaluated for effects on systemic blood pressure in C3H mice. All of the nitroxides studied demonstrated radioprotection compared to saline-treated controls. The 6-membered piperidine ring nitroxides including **Tempol** were reduced to the inactive hydroxylamine rapidly over 10-20 min. The 5-membered ring nitroxides were reduced more slowly over time. The 5-membered ring 3-carbamoyl-PROXYL did not produce a substantial decrease in systemic blood pressure after i.p. administration compared to the other nitroxides studied. 3-Carbamoyl-PROXYL was further evaluated over a range of whole body radiation doses and was found to provide radioprotection. All of the nitroxides studied provided radioprotection. In vivo radioprotection for all of the compds. except 3-carbamoyl-PROXYL may be at least partially explained by the induction of hypotension and bone marrow hypoxia. 3-Carbamoyl-PROXYL provided in vivo radioprotection similar in magnitude to **Tempol** and had little effect on blood pressure compared to the other nitroxides. Other mechanisms for radioprotection, including scavenging of free radicals are likely. 3-Carbamoyl-PROXYL should be evaluated further as a systemic radioprotector.

IT **2226-96-2, Tempol 2896-70-0,** 4-Oxo-tempo
14691-88-4, Tempamine
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in vivo radioprotection and effects on blood pressure of the stable free radical nitroxides)

RE.CNT 9
RE
(1) Hahn, S; Cancer Res 1992, V52, P1750 HCAPLUS
(2) Hahn, S; Free Radic Biol Med 1997, V22, P1211 HCAPLUS
(3) Hahn, S; Radiat Res 1992, V132, P87 HCAPLUS
(5) Mitchell, J; Arch Biochem Biophys 1991, V289, P62 HCAPLUS
(6) Mitchell, J; Biochemistry 1990, V29, P2802 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L96 ANSWER 5 OF 36 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:5873 HCAPLUS
DN 130:206753
TI Redox generation of nitric oxide to radiosensitize hypoxic cells
AU **Mitchell, James B.**; DeGraff, William; Kim, Sungmee; Cook, John A.; Gamson, Janet; Christodoulou, Danae; Feelisch, Martin; Wink, David A.
CS Radiation Biology Branch, National Cancer Institute, Bethesda, MD, 20892, USA
SO Int. J. Radiat. Oncol., Biol., Phys. (1998), 42(4), 795-798
CODEN: IOBPD3; ISSN: 0360-3016
PB Elsevier Science Inc.
DT Journal
LA English
AB Previous studies have shown that nitric oxide (NO) delivered from NO donor agents sensitizes hypoxic cells to ionizing radiation. In the present study, nitroxyl (NO-), a potential precursor to endogenous NO prodn., was evaluated for hypoxic cell radiosensitization, either alone or in combination with electron acceptor agents. Radiation survival curves of Chinese hamster V79 lung fibroblasts under aerobic and hypoxic conditions were assessed by clonogenic assay. Hypoxia induction was achieved by metab.-mediated oxygen depletion in dense cell suspensions. Cells were treated with NO- produced from the nitroxyl donor Angeli's salt (AS, Na2N2O3, sodium trioxodinitrate), in the absence or presence of electron acceptor agents, ferricyanide, or **tempol**. NO concns. resulting from the combination of AS and ferricyanide or **tempol** were measured under hypoxic conditions using an NO-sensitive electrode. Treatment of V79 cells under hypoxic conditions with AS alone did not result in radiosensitization; however, the combination of AS with

ferricyanide or **tempol** resulted in significant hypoxic radiosensitization with SERs of 2.5 and 2.1, resp. Neither AS alone nor AS in combination with ferricyanide or **tempol** influenced aerobic radiosensitivity. The presence of NO generated under hypoxic conditions from the combination of AS with ferricyanide or **tempol** was confirmed using an NO-sensitive electrode. Combining NO- generated from AS with electron acceptors results in NO generation and substantial hypoxic cell radiosensitization. NO- derived from donor agents or endogenously produced in **tumors**, combined with electron acceptors, may provide an important strategy for radiosensitizing hypoxic cells and warrants in vivo evaluation.

IT **2226-96-2, Tempol.**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(redox generation of nitric oxide to radiosensitize hypoxic cells)

RE.CNT 16
RE
(1) Bonner, F; Inorg Chem 1975, V14, P558 HCAPLUS
(3) Hahn, S; Cancer Res 1992, V52, P1750 HCAPLUS
(4) Hobbs, A; Proc Natl Acad Sci USA 1994, V91, P10992 HCAPLUS
(6) Ignarro, L; Ann Rev Pharmacol Toxicol 1990, V30, P535 HCAPLUS
(7) Millar, B; Br J Cancer 1978, V37, P73 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L96 ANSWER 6 OF 36 HCAPLUS COPYRIGHT 2001 ACS
AN 1998:800011 HCAPLUS
DN 130:20564
TI The use of a nitroxide or a **prodrug** thereof in the prophylactic and therapeutic treatment of **cancer**
IN Mitchell, James B.; Russo, Angelo; Deluca, Anne Marie; Cherukuri, Murali Krishna
PA United States Dept. of Health and Human Services, USA
SO PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9853835	A1	19981203	WO 1998-US10685	19980527 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9875987	A1	19981230	AU 1998-75987	19980527 <--
EP 986393	A1	20000322	EP 1998-923772	19980527 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRAI US 1997-47724 19970527 <--
WO 1998-US10685 19980527
OS MARPAT 130:20564
AB A method is provided for the prophylactic and therapeutic treatment of **cancer**. The method comprises administering to an animal, preferably a mammal, more preferably a human, at risk for developing a **cancer** or having a **cancer** a nitroxide or a prodrug thereof, wherein the nitroxide or prodrug thereof, preferably alicyclic or heterocyclic (Markush included), in an amt. sufficient to prevent or treat the **cancer**, wherein the **cancer** is susceptible to prevention or treatment by the nitroxide or prodrug thereof. Also provided is a compn. for use in the method.

IT **2226-96-2, Tempol**
RL: BAC (Biological activity or effector, except adverse); THU

(Therapeutic use); BIOL (Biological study); USES (Uses)
(nitroxide or prodrug thereof for **cancer** treatment)
RE.CNT 4
RE
(1) Monti; PAACR ANNUAL MEETING 1977, V38(0), P193
(2) Monti; PAACR ANNUAL MEETING 1995, V36(0), P387
(3) Monti; PAACR ANNUAL MEETING 1998, V39(0), P90
(4) Us Government; WO 9640127 A 1996 HCAPLUS

L96 ANSWER 7 OF 36 HCAPLUS COPYRIGHT 2001 ACS
AN 1998:774234 HCAPLUS
DN 130:29069
TI Use of **Tempol** in the prevention of **photoaging**
IN Bernstein, Eric
PA Thomas Jefferson University, USA
SO U.S., 5 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5840734	A	19981124	US 1997-851739	19970506 <--

AB A method of preventing photoaging and other types of sun damage by topically applying a compn. contg. **Tempol** is provided. Pharmaceutical compns. comprising **Tempol** for the prevention of photoaging and other types of sun damage are also provided. Homozygous line of transgenic mice expressing the 5.2-kb human elastin promoter linked to a chloramphenicol acetyltransferase (CAT) reporter gene was used. **Tempol** reduced the CAT activity significantly.
IT **2226-96-2, Tempol**
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**Tempol** in prevention of photoaging)
RE.CNT 18
RE
(2) Bissett; Photodermatol Photoimmunol Photomed 1990, V7, P56 HCAPLUS
(3) Chen; J Invest Dermatol 1986, V87, P334 HCAPLUS
(5) Emerit; 1992 HCAPLUS
(6) Frances, C; Int J Dermatol 1984, V23, P166 HCAPLUS
(7) Goffman; Int J Rad Onc Bio Phys 1992, V22, P803 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L96 ANSWER 8 OF 36 HCAPLUS COPYRIGHT 2001 ACS
AN 1998:605437 HCAPLUS
DN 130:20284
TI The nitroxyl radical **Tempol** as a modulator of 6-mercaptopurine toxicity and **antitumor** activity
AU Konovalova, N. P.; D'yachkovskaya, R. F.; Volkova, L. M.; Varfolomeev, V. N.
CS Inst. Khim. Fiz., RAN, Chernogolovka, Russia
SO Vopr. Onkol. (**1996**), 42(3), 57-63
CODEN: VOONAW; ISSN: 0507-3758
PB Eskulap
DT Journal
LA Russian
AB The nitroxyl radical **Tempol** decreased the toxicity of 6-mercaptopurine and potentiated its **antitumor** effect in mice with transplantable **adenocarcinoma** 755. It is suggested that this effect might be due, at least, in part to the antioxidant activity of **Tempol**.
IT **2226-96-2, Tempol**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitroxyl radical **Tempol** as a modulator of 6-mercaptopurine toxicity and **antitumor** activity)

L96 ANSWER 9 OF 36 HCAPLUS COPYRIGHT 2001 ACS
AN 1998:505747 HCAPLUS
DN 129:254346
TI Studies of Structure-Activity Relationship of Nitroxide Free Radicals and Their Precursors as Modifiers Against Oxidative Damage
AU Krishna, Murali C.; DeGraff, William; Hankovszky, Olga H.; Sar, Cecilia P.; Kalai, Tamas; Jeko, Jozsef; **Russo, Angelo; Mitchell, James B.**; Hideg, Kalman
CS Radiation Biology Branch, National Cancer Institute, Bethesda, MD, 20892, USA
SO J. Med. Chem. (1998), 41(18), 3477-3492
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
AB The protective effects of stable nitroxides, as well as their hydroxylamine and amine precursors, have been tested in Chinese hamster V79 cells subjected to H2O2 exposure at fixed concn. or exposure to ionizing radiation. Cytotoxicity was evaluated by monitoring the viability of the cells assessed by the clonogenic assay. The compds. tested at fixed concn. varied in terms of ring size, oxidn. state, and ring substituents. Electrochem. studies were carried out to measure the redox midpoint potentials. The studies show that in the case of protection against H2O2 exposure, the protection was detd. by the ring size, oxidn. state, and redox midpoint potentials. In general the protection factors followed the order nitroxides > hydroxylamines > amines. Both the six-membered ring nitroxides and substituted five-membered ring nitroxides were efficient protectors. For six-membered ring nitroxides, the compds. exhibiting the lowest midpoint potentials exhibited maximal protection. In the case of X-radiation, nitroxides were the most protective though some hydroxylamines were also efficient. The amines were in some cases found to sensitize the toxicity of aerobic radiation exposure. The protection obsd. by the nitroxides was not dependent on the ring size. However, the ring substituents had significant influence on the protection. Compds. contg. a basic side chain were found to provide enhanced protection. The results in this study suggest that these compds. are novel antioxidants which can provide cytoprotection in mammalian cells against diverse types of oxidative insult and identify structural determinants optimal for protection against individual types of damage.
IT **2896-70-0 14691-88-4**
RL: BAC (Biological activity or effector, except adverse); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. and structure-activity relationship of nitroxide free radicals and their precursors as modifiers against oxidative damage)
IT **2226-96-2 2564-83-2**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. and structure-activity relationship of nitroxide free radicals and their precursors as modifiers against oxidative damage)

L96 ANSWER 10 OF 36 HCAPLUS COPYRIGHT 2001 ACS
AN 1998:492857 HCAPLUS
DN 129:211678
TI Nitroxides **tempol** and tempo induce divergent signal transduction pathways in MDA-MB 231 breast cancer cells
AU Suy, Simeng; **Mitchell, James B.**; Ehleiter, Desiree; Haimovitz-Friedman, Adriana; Kasid, Usha
CS Departments of Radiation Medicine and Biochemistry and Molecular Biology, Lombardi Cancer Center, Georgetown University Medical Center, Washington, DC, 20007, USA
SO J. Biol. Chem. (1998), 273(28), 17871-17878
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal

LA English
AB **Tempol** and tempo are stable free radical nitroxides that possess antioxidant properties. In this study, the authors examd. the effects of these compds. on components of the mitogen-activated protein kinase signal transduction cascade. Tempo treatment (15 min) of MDA-MB 231 human breast cancer cells resulted in significant levels of tyrosine phosphorylation of several as yet unidentified proteins compared with equimolar concn. of **tempol** (10 mM). Both compds. caused tyrosine phosphorylation and activation of Raf-1 protein kinase (30 min, 2-3-fold). Interestingly, however, only **tempol** caused increased extracellular signal-regulated kinase 1 activity (2 h, .apprx.3-fold). Tempo, but not **tempol**, potently activated stress-activated protein kinase (2 h, >3-fold). Consistent with these data, **tempol** was noncytotoxic, whereas tempo induced apoptotic cell death (2 h, >50%). Tempo treatment also resulted in significant elevation of ceramide levels at 30 min (54% over control) and 1 h (71% over control) posttreatment, preceding stress-activated protein kinase activation and apoptosis. These data suggest that in the absence of an environmental oxidative stress, **tempol** and tempo elicit distinct cellular signaling pathways. The recognition of the mol. mechanisms of nitroxide action may have important implications for biol. effectiveness of these compds.
IT **2226-96-2, Tempol 2564-83-2,** Tempo
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(antioxidant nitroxides **tempol** and tempo induce divergent signal transduction pathways in MDA-MB 231 breast cancer cells in relation to induction of apoptosis)

L96 ANSWER 11 OF 36 HCAPLUS COPYRIGHT 2001 ACS
AN 1997:607266 HCAPLUS
DN 127:287857
TI **Tempol** inhibits neutrophil and hydrogen peroxide-mediated DNA damage
AU Hahn, Stephen M.; **Mitchell, James B.**; Shacter, Emily
CS Radiation Biology Branch, Division of Clinical Sciences, National Cancer Institute, Bethesda, MD, 20892, USA
SO Free Radical Biol. Med. (**1997**), 23(6), 879-884
CODEN: FRBMEH; ISSN: 0891-5849
PB Elsevier
DT Journal
LA English
AB Inflammatory conditions characterized by neutrophil activation are assocd. with a variety of chronic diseases. Reactive oxygen species are produced by activated neutrophils and produce DNA damage which may lead to tissue damage. Previous studies have shown that activated murine neutrophils induce DNA strand breaks in a target plasmacytoma cell, RIMPC 2394. We studied the effect of a water sol. nitroxide antioxidant, **Tempol**, on murine neutrophil induction of DNA strand breaks in this system. Murine neutrophils were isolated from the peritoneal cavity of BALB/cAn mice after an IP injection of pristane oil. Neutrophils were activated by the phorbol ester PMA and co-incubated with RIMPC 2394 cells. Control alk. elution studies revealed progressive DNA strand breaks in RIMPC cells with time. The addn. of **Tempol** to the incubation mixt. prevented DNA damage in a dose dependent fashion. Five mM **Tempol** provided complete protection. **Tempol** protection against DNA strand breaks was similar for both stimulated neutrophils and exogenously added hydrogen peroxide. Measurement of hydrogen peroxide produced by stimulated neutrophils demonstrated that **Tempol** did not decrease hydrogen peroxide concn. Oxidn. of reduced metals, thereby interfering with the prodn. of hydroxyl radical, is the most likely mechanism of nitroxide protection, although superoxide dismutase (SOD)-like activity and scavenging of carbon-based free radicals may also account for a portion of the obsd. protection. The antioxidant activity of **Tempol** inhibited DNA damage by activated neutrophils. The nitroxides as a class of compds. may have a role in the investigation and modification of inflammatory conditions.

IT **2226-96-2, Tempol**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**tempol** inhibits neutrophil and hydrogen peroxide-mediated DNA damage)

L96 ANSWER 12 OF 36 HCAPLUS COPYRIGHT 2001 ACS
AN 1997:258309 HCAPLUS
DN 126:290156
TI Evaluation of **tempol radioprotection** in a murine **tumor** model
AU Hahn, Stephen M.; Sullivan, Francis J.; **DeLuca, Anne Marie**; Krishna, C. Murali; Wersto, Nancy; Venzon, David; **Russo, Angelo**; **Mitchell, James B.**
CS Radiation Biol. Branch, Natl. Cancer Inst., Bethesda, MD, USA
SO Free Radical Biol. Med. (**1997**), 22(7), 1211-1216
CODEN: FRBMEH; ISSN: 0891-5849
PB Elsevier
DT Journal
LA English
AB **Tempol**, a stable nitroxide free radical compd., is an in vitro and in vivo radioprotector. Previous studies have shown that **Tempol** protects C3H mice against whole-body radiation-induced bone marrow failure. In this study, the radioprotection of **tumor** tissue was evaluated. RIF-1 **tumor** cells were implanted in female C3H mice 10 d prior to radiation. Groups of mice were injected i.p. with **Tempol** (275 mg/kg) or PBS followed 10 min later by a single dose of radiation to the **tumor** bed. **Tumor** growth curves generated after 10 and 33.3 Gy doses of radiation showed no difference in growth between the **Tempol**- and PBS-treated animals. A full radiation dose-response expt. revealed a **tumor** control dose in 50% of the animals in 30 d(TCD50/30) value of 36.7 Gy for **Tempol**-treated mice and 41.8 Gy for saline-treated mice suggesting no protection of the RIF-1 **tumor** by **Tempol**. **Tumor** pharmacokinetics were done to det. why **Tempol** differentially protected bone marrow and not **tumor** cells. Differential redn. of **Tempol** in the RIF-1 **tumor** and bone marrow was evaluated with EPR spectroscopy 10, 20, and 30 min after injection. Bioredn. of **Tempol** to its corresponding hydroxylamine (which is not a radioprotector) occurred to a greater extent in RIF-1 **tumor** cells compared to bone marrow. We conclude that the differences in radioprotection may result from enhanced **intratumor** bioredn. of **Tempol** to its nonradioprotective hydroxylamine analog. The nitroxides as a class of compds. may provide a means to exploit the redox differences between normal tissues and **tumors**.
IT **2226-96-2, Tempol**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**tempol** radioprotection evaluation in murine **tumor** model)

L96 ANSWER 13 OF 36 HCAPLUS COPYRIGHT 2001 ACS
AN 1997:140234 HCAPLUS
DN 126:139898
TI Nitroxides as protectors against **oxidative stress**
IN **Mitchell, James B.**; Samuni, Amran; Degraff, William G.; Hahn, Stephen
PA United States Dept. of Health and Human Services, USA
SO PCT Int. Appl., 50 pp
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI WO 9640127 A1 19961219 WO 1996-US9524 19960607 <--
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RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML
AU 9661028 A1 19961230 AU 1996-61028 19960607 <--
PRAI US 1995-473960 19950607 <--
WO 1996-US9524 19960607 <--
OS MARPAT 126:139898
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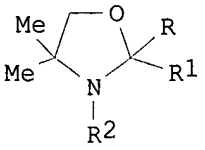

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AB The instant invention is directed to the use of a biol. compatible compn., contg. an effective amt. of a metal-independent nitroxide compd. which is preferably represented by formula (I), wherein R is -CH3; R1 is -C2H5, -C3H7, -C4H9, -C5H11, -C6H13, -CH2-CH(CH3)2, -CHCH3C2H5 or -(CH2)7-CH3, or where R and R1 together form spirocyclopentane, spirocyclohexane, spirocycloheptane, spirocyclooctane, 5-cholestane, or norbornane, R2 is -O., or -OH, or a physiol. acceptable salt thereof, and a pharmaceutically acceptable carrier, as antioxidants capable of protecting cells, tissues, organs, and whole organs against the deleterious effects of harmful free radical species generated during oxidative stress.
IT **2226-96-2, TEMPOL 2564-83-2**, TEMPO
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. and formulation of nitroxides as protectors against oxidative stress)

L96 ANSWER 14 OF 36 HCAPLUS COPYRIGHT 2001 ACS
AN 1996:742585 HCAPLUS
DN 126:14455
TI Modulatory effect of **tempol** on toxicity and **antitumor** activity of 6-mercaptopurine and on P450 cytochrome level
AU Konovalova, N. P.; Diatchkovskaya, R. F.; Volkova, L. M.; Varfolomeev, V. N.
CS Institute Chemical Physics, Russian Academy Sciences, Chernogolovka, 142 432, Russia
SO Neoplasma (**1996**), 43(5), 341-346
CODEN: NEOLA4; ISSN: 0028-2685
PB Slovak Academic Press
DT Journal
LA English
AB Low selectivity of contemporary **antitumor** drugs requires a search for its improvement. In this context, nitroxyl radicals are of interest as promising pharmacol. agents. The introduction of nitroxyl radical into the structure of **antitumor** cytostatics was found to reduce considerably their general and specific toxicity. In this work, the authors demonstrate a detoxifying effect of **tempol** upon its combined injection with cytostatics at their abs. LD in intact mice as well as an improvement of sensitivity of **tumor**-bearing animals to 6-mercaptopurine. **Tempol** is shown to normalize the level of the oxidized form of cytochrome P 450 in liver, which had been reduced as a result of the injection of 6-mercaptopurine.
IT **2226-96-2, Tempol**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)

(modulatory effect of **tempol** on toxicity and **antitumor** activity of cytostatics and on liver cytochrome P 450 level)

L96 ANSWER 15 OF 36 HCAPLUS COPYRIGHT 2001 ACS
AN 1996:644233 HCAPLUS
DN 125:317237
TI Do nitroxide antioxidants act as **scavengers** of superoxide radical or as SOD mimics?
AU Krishna, Murali C.; **Russo, Angelo; Mitchell, James B.**; Goldstein, Sara; Dafni, Hagit; Samuni, Amram
CS Molecular Biolog, Hebrew Univ., Jerusalem, 91120, Israel
SO J. Biol. Chem. (**1996**), 271(42), 26026-26031
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB Stable nitroxide radicals were reported to act as SOD mimics and catalyze the **dismutation** of superoxide radical through two different catalytic pathways including reductive and oxidative reaction mechanisms. Recent studies directly monitoring superoxide radical and employing kinetics anal. did not reveal SOD activity of nitroxides. Such discrepancy may result in cases where distinction of stoichiometric scavengers from catalytic detoxifiers of superoxide radical is not readily feasible. Nitroxides are effective antioxidants that protect against oxidative injury in various pathol. processes. The distinction of their SOD mimic activity from superoxide radical scavenging was established by examg. the validity of direct and indirect methods employed to assay SOD-like catalytic activity. Kinetics anal. along with direct EPR monitoring were used to study the mechanism underlying nitroxide reactions with superoxide radical. The nitroxide EPR signal decayed in the presence of NADH but otherwise did not decrease with time, thus substantiating its catalytic role in superoxide radical **dismutation**. The catalytic rate consts. for superoxide radical **dismutation**, detd. for the nitroxides tested, were found to increase with [H+], indicating that .bul.OOH rather than superoxide radical is oxidizing the nitroxide. The results demonstrate the limitations assocd. with direct kinetics anal. in evaluating SOD mimic activity, underscoring the need for independent assays for valid discrimination of SOD mimics from stoichiometric scavengers of superoxide radical.
IT **2226-96-2**, 4-**Hydroxy**-2,2,6,6-**tetramethylpiperidine**-1-**oxyl 2564-83-2**, 2,2,6,6-Tetramethylpiperidine-1-oxyl
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(nitroxide antioxidants as scavengers of superoxide radical or as SOD mimics)

L96 ANSWER 16 OF 36 HCAPLUS COPYRIGHT 2001 ACS
AN 1996:644232 HCAPLUS
DN 125:295936
TI Stimulation by nitroxides of catalase-like activity of hemeproteins. Kinetics and mechanism
AU Krishna, Murali C.; Samuni, Amram; Taira, Junsei; Goldstein, Sara; **Mitchell, James B.; Russo, Angelo**
CS Radiation Biology Branch, National Institutes of Health, Bethesda, MD, 20892, USA
SO J. Biol. Chem. (**1996**), 271(42), 26018-26025
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB The ability of stable nitroxide radicals to detoxify hypervalent heme proteins such as ferrylmyoglobin (MbFeIV) produced in the reaction of metmyoglobin (MbFeIII) and H2O2 was evaluated by monitoring O2 evolution, H2O2 depletion, and redox changes of the heme prosthetic group. The rate of H2O2 depletion and O2 evolution catalyzed by MbFeIII was enhanced by stable nitroxides such as 4-OH-2,2,6,6-tetramethyl-piperidinoxyl (TPL) in a catalytic fashion. The redn. of MbFeIV to MbFeIII enhanced

catalase-like activity more than 4-fold. During dismutation of H2O2, [TPL] and [MgFeIV] remained const. NADH caused: (a) inhibition of H2O2 decay; (b) progressive redn. of TPL to its resp. hydroxylamine TPL-H; and (c) arrest/inhibition of oxygen evolution or elicit consumption of O2. Following depletion of NADH the evolution of O2 resumed and the initial concn. of TPL was restored. Kinetic anal. showed that two distinct forms of MbFeIV might be involved in the process. In summary, by shuttling between two oxidn. states, namely nitroxide and oxoammonium cation, stable nitroxides enhance the catalase mimic activity of MbFeIII, thus facilitating H2O2 dismutation accompanied by O2 evolution and providing protection against hypervalent heme proteins.

IT **2226-96-2**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(stimulation by nitroxides of catalase-like activity of hemeproteins. Kinetics and mechanism)

L96 ANSWER 17 OF 36 HCAPLUS COPYRIGHT 2001 ACS
AN 1996:299892 HCAPLUS
DN 125:543
TI Adjunctive treatment of murine **neuroblastoma** with 6-hydroxydopamine and **tempol**
AU Purpura, Patti; Westman, Laurel; Will, Patricia; Eidelman, Anthony; Kagan, Valerian E.; Osipov, Anatoly N.; Schor, Nina Felice
CS Dep. Pediatrics, Neurology, Pharm., Environ., Occupational Toxicology, Univ. Pittsburgh, Pittsburgh, PA, 15213, USA
SO Cancer Res. (**1996**), 56(10), 2336-2342
CODEN: CNREA8; ISSN: 0008-5472
DT Journal
LA English
AB Currently available therapy for disseminated neuroblastoma affords only a 5-20% 5-yr survival rate. We have attempted to design targeted chemotherapy for this disease by exploiting the dopamine uptake system on neuroblastoma cells. 6-Hydroxydopamine (6OHDA) is a neurotransmitter analog, which generates cytolytic oxygen radicals in neuroblastoma cells that take it up. It is, however, predictably, systemically toxic, because of its spontaneous oxidn. It toxicity is particularly severe in the sympathetic nervous system, because this tissue selectively concs. dopamine and its analogs. Lowering the dose of 6OHDA below toxic levels prohibitively compromises its **antitumor** effect. To avoid both the systemic and sympathetic nervous system toxicity yet retain the **antitumor** efficacy of 6OHDA, we have used the antioxidant **Tempol** adjunctively with 6OHDA. Administration of **Tempol** (250 mg/kg, i.p.) 10 min prior to administration of toxic doses of 6OHDA (350 or 400 mg/kg, i.p.) resulted in a decrease in the mortality rate, sympathetic nervous system impairment, and activity impairment compared with those seen with 6OHDA alone. **Tumor** wts. from mice administered saline or **Tempol** alone were 3.6 .+-. 1.9 and 2.9 .+-. 0.7 g, resp. In contrast, mice administered **Tempol** followed by 6OHDA had an av. **tumor** wt. of 0.7 .+-. 0.3 g. **Tumor** incidence was also reduced from 80-100% to 40%. Studies performed using ESR spectroscopy suggest that **Tempol** acts in this system by reacting directly with both the 6OHDA radical and, in the presence of iron, its oxidn. product, the hydroxyl radical.

IT **2226-96-2, Tempol**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(adjunctive treatment of murine neuroblastoma with 6-hydroxydopamine and **tempol**)

L96 ANSWER 18 OF 36 HCAPLUS COPYRIGHT 2001 ACS
AN 1995:586969 HCAPLUS
DN 123:78627
TI Protection from radiation-induced chromosomal aberrations by the nitroxide **Tempol**

AU Johnstone, Peter A. S.; DeGraff, William G.; **Mitchell, James B.**
CS Radiation Biology Branch, National Cancer Institute, Bethesda, MD, USA
SO Cancer (Philadelphia) (**1995**), 75(9), 2323-7
CODEN: CANCAR; ISSN: 0008-543X
DT Journal
LA English
AB The nitroxide **Tempol** (4-**hydroxy**-2,2,6,6-**tetramethylpiperidine**-1-**oxyl**) is a stable, free radical that exhibits protection from ionizing radiation damage and from oxidative stress mediated through exposure of cells to superoxide or hydrogen peroxide. Radiation protection has been obsd. in both in vivo and in vitro models. To understand the mechanism of **Tempol**-mediated radioprotection better, the prodn. of radiation induced chromosome aberrations was evaluated. This study analyzed **Tempol**-mediated radioprotection of human peripheral blood lymphocytes (PBLs). Peripheral blood lymphocytes were exposed to control (0mM), 10 mM (Tp10), and 50 mM (Tp50) concns. of **Tempol** for 20 min before irradn. with 0, 150, 300, and 450 cGy. One quarter mL whole blood was cultured in F12 medium and phytohemagglutinin at 37.degree. for 49, 54, 59, and 64 h. Colcemid was added to each sample for the last 5 h before harvest. Cells were harvested, treated with hypotonic soln., and fixed before dropping on cold clean slides. Mitotic indexes and frequency of dicentric, ring, and triradial chromosomal aberrations were detd. at 1000.times. magnification for each treatment group at each collection point. Treatment of cells with **Tempol** alone did not induce the chromosomal aberration frequency above that for unirradiated controls. Radiation dose response curves for total chromosome aberration prodn. revealed radioprotection for **Tempol** treatment for both 10 and 50 mM exposures. **Tempol** protection factors (assessed at 0.2 aberrations/cell level) for Tp 10 and Tp 50 were 2.2 and 2.8, resp. **Tempol** protects against radiation-induced chromosome aberrations in human PBLs. This finding is consistent with and lends support to previous studies in which **Tempol** was reported to enhance cell survival and reduce radiation-induced DNA double strand breaks.
IT **2226-96-2, Tempol**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(protection from radiation-induced chromosomal aberrations by nitroxide **Tempol**)

L96 ANSWER 19 OF 36 HCAPLUS COPYRIGHT 2001 ACS
AN 1995:584888 HCAPLUS
DN 123:4740
TI Neurophysiological consequences of nitroxide antioxidants
AU Hahn, Stephen M.; Lepinski, Dennis L.; **DeLuca, Anne Marie; Mitchell, James B.**; Pellmar, Terry C.
CS Div. Cancer Treatment, Natl. Cancer Inst., Bethesda, MD, 20892, USA
SO Can. J. Physiol. Pharmacol. (**1995**), 73(3), 399-403
CODEN: CJPPA3; ISSN: 0008-4212
DT Journal
LA English
AB Nitroxides are antioxidant compds. that have been shown to provide radioprotection in vivo and in vitro. Radioprotection in vivo is limited by toxicity, which appears to be neurol. in nature. To further evaluate the toxicity of these compds., 3 representative nitroxides: **Tempol**, Tempamine, and Tempo, were examd. in slices of guinea pig hippocampus. Each nitroxide increased the population spike and potentiated excitatory postsynaptic potential-spike coupling. Repetitive activity and epileptiform activity were obsd. at the highest concns. of Tempo and Tempamine used. **Tempol** was the least toxic compd. in this system, followed by Tempamine and Tempo.
IT **2226-96-2, Tempol 2564-83-2,** Tempo
14691-88-4, Tempamine
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(neurophysiol. effects of nitroxide antioxidants)

L96 ANSWER 20 OF 36 HCAPLUS COPYRIGHT 2001 ACS
AN 1994:211569 HCAPLUS
DN 120:211569
TI Protection from lethal irradiation by the combination of stem cell factor and **tempol**
AU Liebmann, James; **DeLuca, Anne Marie**; Epstein, Alan; Steinberg, Seth M.; Morstyn, George; **Mitchell, James B.**
CS Radiobiol. Sec., Natl. Cancer Inst., Bethesda, MD, 20892, USA
SO Radiat. Res. (**1994**), 137(3), 400-4
CODEN: RAREAE; ISSN: 0033-7587
DT Journal
LA English
AB Cytokines that stimulate growth and differentiation of hematopoietic precursor cells have been used as protectors in vivo against ionizing radiation. Recently, the authors have shown that the nitroxide **tempol** is also an effective radiation protector in vivo. The purpose of the present study was to det. if the combination of **tempol** with stem cell factor (SCF, c-kit ligand) would provide enhanced radiation protection in C57 mice compared with the protection afforded by either agent alone. Mice were exposed to whole-body .gamma.-irradn. and assessed for survival at 30 days after irradn. No control mice survived doses of >9 Gy. Treatment of mice before and after radiation with SCF alone (100 .mu.g/kg at -20 h, -4 h and +4 h) protected mice from radiation at doses of as high as 10 Gy (76% survival). **Tempol** (350 mg/kg) given 10 min prior to radiation was a radioprotector at 9 Gy (55% survival). The combination of SCF and **tempol** increased the survival of mice exposed to radiation doses up to 11 Gy (32% survival for the combination vs 4% for SCF alone and 0% for **tempol** alone; $P < 0.001$ for the combination vs either agent alone). Lower doses of SCF alone (1 .mu.g/kg) or **tempol** alone (275 mg/kg) did not protect mice from radiation. However, the combination of these reduced doses of SCF and **tempol** protected mice from lethal irradn. at 10 Gy. Stem cell factor and **tempol** given either singly or together were well tolerated by the animals. These data show that SCF and **tempol** are radiation protectors and that their radioprotective effects are more then additive when the agents are given together.
IT **2226-96-2, Tempol**
RL: BIOL (Biological study)
(radioprotection by stem cell factor and, of survival from .gamma.-rays)

L96 ANSWER 21 OF 36 HCAPLUS COPYRIGHT 2001 ACS
AN 1993:73248 HCAPLUS
DN 118:73248
TI Nitroxide-mediated protection against x-ray- and neocarzinostatin-induced DNA damage
AU DeGraff, William G.; Krishna, Murali C.; Kaufman, Dwight; **Mitchell, James B.**
CS Radiat. Oncol. Branch, Natl. Cancer Inst., Bethesda, MD, 20892, USA
SO Free Radical Biol. Med. (**1992**), 13(5), 479-87
CODEN: FRBMEH; ISSN: 0891-5849
DT Journal
LA English
AB The stable free radical **Tempol** (4-hydroxy-2,2,6,6-tetramethylpiperidinyloxy) has been shown to protect against x-ray-induced cytotoxicity and hydrogen- or xanthine oxidase-induced cytotoxicity and mutagenicity. The ability of **Tempol** to protect against x-ray- or neocarzinostatin (NCS)-induced mutagenicity or DNA double-strand breaks (dsb) was studied in Chinese hamster cells. **Tempol** (50 mM) provided a protection factor of 2.7 against x-ray-induced mutagenicity in Chinese hamster ovary (CHO) AS52 cells, with a protection factor against cytotoxicity of 3.5. Using the field inversion gel electrophoresis technique of measuring DNA dsb, 50 mM **Tempol** provides a threefold redn. in DNA damage at an x-ray dose of 40 Gy. For NCS-induced damage, **Tempol** increased survival from 9% to 80% at 60 ng/mL NCS

and reduced mutation induction by a factor of approx. 3. DNA dsb were reduced by a factor of approx. 7 at 500 ng/mL NCS. **Tempol** is representative of a class of stable nitroxide free radical compds. that have superoxide dismutase-mimetic activity, can oxidize metal ions such as ferrous iron that are complexed to DNA, and may also detoxify radiation-induced organoperoxide radicals by competitive scavenging. The NCS chromophore is reduced by sulfhydryls to an active form. Electron resonance (ESR) spectroscopy shows that 2-mercaptoethanol-activated NCS reacts with **Tempol** 3.5 times faster than does unactivated NCS. Thus, **Tempol** appears to inactivate the NCS chromophore before a substantial amt. of DNA damage occurs.

IT **2226-96-2, Tempol**
RL: BIOL (Biological study)
(x-ray- and neocarzinostatin-induced DNA damage prevention by)

L96 ANSWER 22 OF 36 HCAPLUS COPYRIGHT 2001 ACS
AN 1992:629205 HCAPLUS
DN 117:229205
TI Identification of nitroxide radioprotectors
AU Hahn, Stephen M.; Wilson, Lynn; Krishna, C. Murali; Liebmann, James; DeGraff, William; Gamson, Janet; Samuni, Amram; Venzon, David; **Mitchell, James B.**
CS Radiobiol. Sect., Natl. Cancer Inst., Bethesda, MD, 20892, USA
SO Radiat. Res. (**1992**), 132(1), 87-93
CODEN: RAREAE; ISSN: 0033-7587
DT Journal
LA English
AB The nitroxide **Tempol**, a stable free radical, has recently been shown to protect mammalian cells against several forms of oxidative stress including radiation-induced cytotoxicity. To extend this observation, 6 addnl. water-sol. nitroxides with different structural features were evaluated for potential radioprotective properties using Chinese hamster V79 cells and clonogenic assays. Nitroxides (10 mM) were added 10 min prior to radiation exposure and full radiation dose-response curves were detd. In addn. to **Tempol**, 5 of the 6 nitroxides afforded in vitro radioprotection. The best protectors were found to be the pos. charged nitroxides, Tempamine and 3-aminomethyl-PROXYL, with protection factors of 2.3 and 2.4, resp., compared with **Tempol**, which had a protection factor of 1.3. 3-Carboxy-PROXYL, a neg. charged nitroxide, provided minimal protection. DNA binding characteristics as studied by nonequil. dialysis of DNA with each of the nitroxides demonstrated that Tempamine and 3-amino-methyl-PROXYL bound more strongly to DNA than did **Tempol**. Since DNA is assumed to be the target of radiation-induced cytotoxicity, differences in protection may be explained by variabilities in affinity of the protector for the target. This study establishes nitroxides as a general class of new nonthiol radioprotectors and suggests other parameters that may be exploited to find even better nitroxide-induced radioprotection.

IT **2226-96-2, Tempol 2896-70-0**, 4-Oxo-TEMPO
14691-88-4, Tempamine
RL: BIOL (Biological study)
(radioprotection by, of V79 cells survival from x-rays, DNA binding in relation to)

L96 ANSWER 23 OF 36 HCAPLUS COPYRIGHT 2001 ACS
AN 1992:587174 HCAPLUS
DN 117:187174
TI Oxoammonium cation intermediate in the nitroxide-catalyzed dismutation of superoxide
AU Krishna, Murali C.; Grahame, David A.; Samuni, Amram; **Mitchell, James B.**; **Russo, Angelo**
CS Div. Cancer Treatment, Natl. Cancer Inst., Bethesda, MD, 20892, USA
SO Proc. Natl. Acad. Sci. U. S. A. (**1992**), 89(12), 5537-41
CODEN: PNASA6; ISSN: 0027-8424
DT Journal
LA English

AB The dismutation of superoxide (O2-) has previously been shown to be catalyzed by stable nitroxide compds. In the present study, the mechanism of O2- dismutation by various 5- and 6-membered ring nitroxides as superoxide dismutase mimics was studied by ESR spectrometry, UV-visible spectrophotometry, cyclic voltammetry, and bulk electrolysis. ESR signals from the carbocyclic nitroxide derivs. (piperidinyl, pyrrolidinyl, and pyrrolinyl) were unchanged when exposed to enzymically generated O2-, whereas, in the presence of O2- and reducing agents such as NADH and NADPH, the nitroxides underwent redn. to their resp. hydroxylamines. The reaction of 4-hydroxy-2,2,6,6-**tetramethyl**-1-**hydroxypiperidine** (**Tempol**-H) with O2- was measured and, in agreement with earlier reports on related compds., the rate was found to be too slow to be consistent with a mechanism of O2- dismutation involving the hydroxylamine as an intermediate. Voltammetric analyses of the carbocyclic nitroxide derivs. revealed a reversible 1-electron redox couple at pos. potentials. In contrast, oxazolidine derivs. were irreversibly oxidized. At neg. potentials, all of the nitroxides studied exhibited a broad, irreversible reductive wave. The rate of O2- dismutation correlated with the reversible midpoint redox potential. Bulk electrolysis at pos. potentials was found to generate a metastable oxidized form of the nitroxide. The results indicated that the dismutation of O2- is catalyzed by the oxoammonium/nitroxide redox couple for carbocyclic nitroxide derivs. In addn. to the 1-electron mitochondrial redn. pathway, the present results suggested the possibility that cellular bioredn. by a 2-electron pathway may occur subsequent to oxidn. of stable nitroxides. Furthermore, the cellular destruction of persistent spin adduct nitroxides may also be facilitated by a primary univalent oxidn.

IT **2226-96-2**, **Tempol** **2564-83-2**, Tempo
2896-70-0, Tempone **14691-88-4**, Tempamine
RL: BIOL (Biological study)
(superoxide dismutation by, kinetics and mechanism of, redox potential in relation to)

L96 ANSWER 24 OF 36 HCAPLUS COPYRIGHT 2001 ACS
AN 1992:420023 HCAPLUS
DN 117:20023
TI Mechanisms of hypoxic and aerobic cytotoxicity of mitomycin C in Chinese hamster V79 cells
AU Krishna, Murali C.; DeGraff, William; Tamura, Shinji; Gonzalez, Frank J.; Samuni, Amram; **Russo, Angelo; Mitchell, James B.**
CS Radiat. Oncol. Branch, Natl. Cancer Inst., Bethesda, MD, 20892, USA
SO Cancer Res. (**1991**), 51(24), 6622-8
CODEN: CNREA8; ISSN: 0008-5472
DT Journal
LA English
AB Mitomycin C (MMC) induced aerobic and hypoxic cytotoxicity in Chinese hamster V79 cells was studied to evaluate the role of the 1-electron vs. 2-electron reductive bioactivation. Superoxide dismutase, catalase, and desferal had no protective effects on the aerobic or hypoxic cytotoxicity of MMC, whereas **Tempol** and **Tempol**-H, which are known to interrupt and terminate radical reactions, provided partial protection under aerobic conditions. However, under hypoxic conditions, **Tempol** provided complete protection whereas **Tempol**-H was ineffective. ESR and spin-trapping investigations, designed to study the mechanisms of such protective effects, confirmed that MMC is activated by the human NADPH:cytochrome P 450 oxidoreductase to its semiquinone radical and that under aerobic conditions, the semiquinone radical reduces mol. oxygen. Under hypoxic conditions, the semiquinone of MMC reduces H2O2 to produce OH radicals as detected by ESR-spin trapping with 5,5-dimethyl-1-pyrroline N-oxide. The 1-electron reduced product of MMC was also found to reduce **Tempol** to the hydroxylamine. **Tempol**-H, whereas oxidn. of **Tempol**-H by MMC- was negligible. Cell survival studies and ESR observations indicate that the hypoxic cytotoxicity of MMC is mediated by 1-electron activation to its semiquinone intermediate. Under aerobic conditions, the steady state

concn. of this intermediate is low due to the facile autoxidn. of the semiquinone producing O2- and H2O2 which are capable of causing oxidative cytotoxicity. **Tempol**, which can accept an electron from reducing radical species, completely inhibited the hypoxic cytotoxicity of MMC indicating MMC-, the semiquinone of MMC as the species responsible for DNA alkylation and selective hypoxic cytotoxicity of MMC. The results also indicate that the aerobic cytotoxicity is mediated by other processes in addn. to the 1-electron mediated activation.

IT **2226-96-2, Tempol**
RL: BIOL (Biological study)
(mitomycin C hypoxic and aerobic cytotoxicity response to, bioreductive activation in relation to)

L96 ANSWER 25 OF 36 HCAPLUS COPYRIGHT 2001 ACS
AN 1992:251168 HCAPLUS
DN 116:251168
TI Topical application of nitroxide protects radiation-induced alopecia in guinea pigs
AU Goffman, Thomas; Cuscela, Daniel; Glass, Joseph; Hahn, Stephen; Krishna, C. Murali; Lupton, George; **Mitchell, James B.**
CS Radiat. Oncol. Branch, Natl. Cancer Inst., Bethesda, MD, 20892, USA
SO Int. J. Radiat. Oncol., Biol., Phys. (**1992**), 22(4), 803-6
CODEN: IOBPD3; ISSN: 0360-3016
DT Journal
LA English
AB Treatment of Chinese hamster V79 cells with stable nitroxide radical **TEMPOL** (4-**hydroxy**-2,2,6,6-**tetramethylpiperidine**-1-**oxyl**) afforded significant protection against superoxide, hydrogen peroxide, and x-ray mediated cytotoxicity. Radiation-induced alopecia is a common radiotherapeutic problem. Topical application of **TEMPOL** was evaluated for possible protective effects against radiation-induced alopecia using guinea pig skin as a model. For single acute x-ray doses up to 30 Gy, **TEMPOL**, when topically applied 15 min prior to irradn. provided a marked increase in the rate and extent of new hair recovery when compared to untreated skin. **TEMPOL** was detected in treated skin specimens with ESR spectroscopy. Similar measurements of blood samples failed to show any signal resulting from topical application, nor could **TEMPOL** be detected in brain tissue after application on the scalp. **TEMPOL** represents a new class of compds. with potential for selective cutaneous radioprotection without systemic absorption.

IT **2226-96-2, TEMPOL**
RL: BIOL (Biological study)
(radioprotection by, against alopecia from x-ray)

L96 ANSWER 26 OF 36 HCAPLUS COPYRIGHT 2001 ACS
AN 1992:120385 HCAPLUS
DN 116:120385
TI DNA synthesis inhibition by nitroxide radicals in **leukemia** cells
AU Liu, Lisheng; Zheng, Rongliang; Swartz, Harold M.; Zhang, Ziyi; Wei, Lulin
CS Dep. Biol., Lanzhou Univ., Lanzhou, 730000, Peop. Rep. China
SO Sci. China, Ser. B (**1991**), 34(9), 1063-9
CODEN: SCBSE5; ISSN: 1001-652X
DT Journal
LA English
AB Of 10 nitroxide-radical compds. tested, the most active in inhibiting DNA synthesis by and viability of isolated leukemia 7712 cells was 4-isothiocyanato-2,2,6,6-tetramethylpiperidine-1-oxyl. At 2.2 .mu.g/mL it inhibited cellular DNA formation by 50%. The inhibition by this compd., which contains both isothiocyanate and nitroxide groups, was greater than the sum of the inhibition by compds. contg. either of these groups alone. Redn. of the nitroxide moiety to hydroxylamine abolished the ability to inhibit DNA synthesis.

IT **2226-96-2**
RL: BIOL (Biological study)
(DNA formation by leukemia cells inhibition by, structure in relation

to)

L96 ANSWER 27 OF 36 HCAPLUS COPYRIGHT 2001 ACS
AN 1992:100912 HCAPLUS
DN 116:100912
TI **Antimutagenicity** of a low molecular weight superoxide dismutase mimic against oxidative **mutagens**
AU DeGraff, William G.; Krishna, Murali C.; **Russo, Angelo; Mitchell, James B.**
CS Radiobiol. Sect., Natl. Cancer Inst., Bethesda, MD, 20892, USA
SO Environ. Mol. Mutagen. (**1992**), 19(1), 21-6
CODEN: EMMUEG; ISSN: 0893-6692
DT Journal
LA English
AB A set of stable nitroxide free radicals that are used as spin labels have been shown to possess metal-independent superoxide dismutase-like activity. Unlike superoxide dismutase (SOD), these compds. are low mol. wt., and readily penetrate into the cell. A representative nitroxide, 4-hydroxy-2,2,6,6-tetramethylpiperidinyloxy (**Tempol**), was investigated for **antimutagenic** activity in the XPRT forward **mutation** assay in CHO AS52 cells. AS52 cells were exposed to hydrogen peroxide, or the hypoxanthine/xanthine oxidase superoxide generating system, in the presence or absence of 10 mM **Tempol**. **Tempol** itself was not **mutagenic** or toxic to AS52 cells. **Tempol** protected cells nearly completely from the cytotoxic and **mutagenic** effects of hydrogen peroxide and hypoxanthine/xanthine oxidase. It is suggested that the **antimutagenic** activity of **Tempol** is an intracellular phenomenon.
IT **2226-96-2, Tempol**
RL: BIOL (Biological study)
(active oxygen species cytotoxicity and **mutagenicity** in animal cell prevention by, superoxide dismutase mimic in relation to)

L96 ANSWER 28 OF 36 HCAPLUS COPYRIGHT 2001 ACS
AN 1991:577284 HCAPLUS
DN 115:177284
TI Nitroxides as protectors against oxidative stress
IN **Mitchell, J. B.**; Samuni, A.; DeGraff, W. G.; Hahn, S.
PA National Institutes of Health, USA
SO U. S. Pat. Appl., 38 pp. Avail. NTIS Order No. PAT-APPL-7-494 532.
CODEN: XAXXAV
DT Patent
LA English
FAN.CNT 1

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	CA 2078287	AA	19910917	CA 1991-2078287	19910318	<--
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	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE					
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OS MARPAT 115:177284

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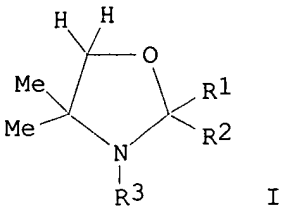


I

AB Oxazole derivs. I (R1 = Me; R2 = Et, Pr, Bu, etc.; R1 with R2 = spirocyclopentane, spirocyclohexane, etc.; R3 = O, OH) and other nitroxides, e.g. **Tempol**, are used to protect animal tissues against oxidative stress. Thus, 2-spirocyclohexane-5,5-dimethyl-3-oxazolidinoxyl (prepn. described) protected Chinese hamster V79 cells exposed to hypoxanthine/xanthine oxidase. **Tempol** protected female C3H mice from whole body irradn.; radiation LD50 was increased approx. 25%. The compds. act as superoxide dismutase mimics.

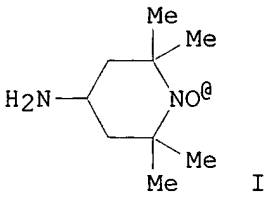
IT **2226-96-2, Tempol**
RL: BIOL (Biological study)
(as radioprotectant and biol. antioxidant)

L96 ANSWER 29 OF 36 HCAPLUS COPYRIGHT 2001 ACS
AN 1991:488366 HCAPLUS
DN 115:88366
TI Inhibition of oxygen-dependent radiation-induced damage by the nitroxide superoxide dismutase mimic, **tempol**
AU **Mitchell, James B.**; DeGraff, William; Kaufman, Dwight; Krishna, Murali C.; Samuni, Amram; Finkelstein, Eli; Ahn, Min S.; Hahn, Stephen M.; Gamson, Janet; **Russo, Angelo**
CS Radiat. Oncol. Branch, Natl. Cancer Inst., Bethesda, MD, 20892, USA
SO Arch. Biochem. Biophys. (**1991**), 289(1), 62-70
CODEN: ABBIA4; ISSN: 0003-9861
DT Journal
LA English
AB Stable nitroxide radicals have been previously shown to function as superoxide dismutase (SOD) mimics and to protect mammalian cells against superoxide and H2O2-mediated oxidative stress. These unique characteristics suggested that nitroxides, such as 4-**hydroxy**-2,2,6,6-**tetramethylpiperidine**-1-**oxyl** (**Tempol**), might protect mammalian cells against ionizing radiation. Treating Chinese hamster cells under aerobic conditions with 5, 10, 50, and 100 mM **Tempol** 10 min prior to x-rays resulted in radiation protection factors of 1.25, 1.30, 2.1, and 2.5, resp. However, the reduced form of **Tempol** afforded no protection. **Tempol** treatment under hypoxic conditions did not provide radioprotection. Aerobic x-ray protection by **Tempol** could not be attributed to the induction of intracellular hypoxia, increase in intracellular glutathione, or induction of intracellular SOD mRNA. **Tempol** thus represents a new class of non-thiol-contg. radiation protectors, which may be useful in elucidating the mechanism(s) of radiation-induced cellular damage and may have broad applications in protecting against oxidative stress.

IT **2226-96-2, Tempol**
RL: BIOL (Biological study)
(radioprotection by, of V-79 cell survival from x-rays, oxygen dependence of)

L96 ANSWER 30 OF 36 HCAPLUS COPYRIGHT 2001 ACS
AN 1991:486966 HCAPLUS
DN 115:86966

TI Nitroxide stable radicals protect beating cardiomyocytes against oxidative damage
AU Samuni, Amram; Winkelsberg, Dorit; Pinson, Arie; Hahn, Stephen M.; **Mitchell, James B.; Russo, Angelo**
CS Sch. Med., Hebrew Univ., Jerusalem, 91010, Israel
SO J. Clin. Invest. (**1991**), 87(5), 1526-30
CODEN: JCINAO; ISSN: 0021-9738
DT Journal
LA English
GI



I

AB The protective effect of stable nitroxide radicals (e.g., I) against oxidative damage was studied using cardiomyocyte cultures obtained from newborn rats. Monolayered cardiomyocytes were exposed to H2O2 and the effect on spontaneous beating and leakage of LDH was detd. H2O2 irreversibly blocked rhythmic beating and resulted in a significant membrane injury as shown by the release of LDH. The injury was prevented by catalase which removes H2O2 and by cell-permeable, metal-chelating agents such as desferrioxamine or bipyridine. In contrast, reagents which are excluded from the cell such as superoxide dismutase or DTPA did not protect the cells against H2O2. Five- and 6-membered ring, stable nitroxide radicals which have previously been shown to chem. act as low-mol.-wt., membrane-permeable, SOD-mimetic compds. provide full protection. The nitroxides prevented leakage of LDH and preserved normal cardiomyocyte contractility, presumably by intercepting intracellular O radicals. Alternatively, protection may result through nitroxides reacting with reduced transition metal ions or by detoxifying secondary org. radicals.
IT **2226-96-2, Tempol 2564-83-2**, Tempo
14691-88-4, Tempamine
RL: BIOL (Biological study)
(heart beat response to)

L96 ANSWER 31 OF 36 HCAPLUS COPYRIGHT 2001 ACS
AN 1991:485377 HCAPLUS
DN 115:85377
TI Nitroxide SOD-mimics: modes of action
AU Samuni, Amram; **Mitchell, James B.**; DeGraff, William; Krishna, C. Murali; Samuni, Uri; **Russo, Angelo**
CS Radiat. Oncol. Branch, Natl. Cancer Inst., Bethesda, MD, 20892, USA
SO Free Radical Res. Commun. (**1991**), 12-13(Pt. 1), 187-94
CODEN: FRRCEX; ISSN: 8755-0199
DT Journal
LA English
AB Low mol. wt. superoxide dismutase mimics have been shown to afford protection from oxidative damage. Such SOD-mimics can readily permeate cell membrane achieving sufficiently high levels both inside and outside the cell to effectively detoxify intracellular O2. Preliminary findings also indicated that metal-based and metal-free SOD-mimics can protect hypoxic cells from H2O2-induced damage. The present study explored the possibility that SOD-mimics such as desferrioxamine-Mn(III) chelate [DF-Mn] or cyclic nitroxide stable free radicals could protect from O2-independent damage. Killing of monolayered V79 Chinese hamster cells were induced by H2O2 or by tert-Bu hydroperoxide (t-BHP) and assayed clonogenically. Neither catalase nor native SOD protected the cells from

t-BHP. In contrast, both DF-Mn and cyclic nitroxides protected suggesting cytotoxic processes independent of O2 or of O2-derived active species. The inhibition of the damage by both metal-free and metal-based SOD mimics is attributable to either SOD-mimic reacting with reduced transition metal to block the Fenton reaction and/or intercepting and detoxifying intracellular org. free radicals.

IT **2226-96-2**, 4-**Hydroxy**-2,2,6,6-**tetramethylpiperidine**-1-**oxyl**
RL: PRP (Properties)
(cytoprotective effect of, as superoxide dismutase mimic)

L96 ANSWER 32 OF 36 HCAPLUS COPYRIGHT 2001 ACS
AN 1991:464685 HCAPLUS
DN 115:64685
TI SOD-like activity of 5-membered ring nitroxide spin labels
AU Samuni, Amram; Min, Ahn; Krishna, C. Murali; **Mitchell, James B.**; **Russo, Angelo**
CS Div. Cancer Treat., NCI, Bethesda, MD, 20892, USA
SO Adv. Exp. Med. Biol. (**1990**), 264(Antioxid. Ther. Prev. Med.), 85-92
CODEN: AEMBAP; ISSN: 0065-2598
DT Journal
LA English
AB The hydroxylamine, 2-ethyl-1-hydroxy-2,5,5-trimethyl-3-oxazolidinoxyl (OXANO), has superoxide dismutase (SOD)-like activity and protects mammalian cells against oxidative damage. The radical-radical reaction between stable nitroxide and O2-.bul. is not limited to OXANO but is shared by other nitroxides which exhibit, therefore, SOD-like activity. Despite differences in charge, size, nd lipophilicity the nitroxides studied readily react with O2-.bul..
IT **2226-96-2 2564-83-2 14691-88-4**
RL: BIOL (Biological study)
(superoxide dismutase-like activity of, structure in relation to)

L96 ANSWER 33 OF 36 HCAPLUS COPYRIGHT 2001 ACS
AN 1991:57081 HCAPLUS
DN 114:57081
TI Nitroxides block DNA scission and protect cells from oxidative damage
AU Samuni, Amram; Godinger, Dina; Aronovitch, Jacob; **Russo, Angelo**; **Mitchell, James B.**
CS Sch. Med., Hebrew Univ., Jerusalem, 91010, Israel
SO Biochemistry (**1991**), 30(2), 555-61
CODEN: BICHAW; ISSN: 0006-2960
DT Journal
LA English
AB The protective effect of cyclic stable nitroxide free radicals, having SOD-like activity, against oxidative damage was studied by using Escherichia coli xthA DNA repair-deficient mutant hypersensitive to H2O2. Oxidative damage induced by H2O2 was assayed by monitoring cell survival. The metal chelator 1,10-phenanthroline (OP), which readily interchelates into DNA, potentiated the H2O2-induced damage. The extent of in vivo DNA scission and degrdn. was studied and compared with the loss of cell viability. The extent of DNA breakage correlated with cell killing, supporting previous suggestions that DNA is the crucial cellular target of H2O2 cytotoxicity. The xthA cells were protected by catalase but not by superoxide dismutase (SOD). Both five- and six-membered ring nitroxides, having SOD-like activity, protected growing and resting cells from H2O2 toxicity, without lowering H2O2 concn. To check whether nitroxides protect against O2.bul.--independent injury also, the expts. were repeated under hypoxia. These nitroxides also protected hypoxic cells against H2O2, suggesting alternative modes of protection. Since nitroxides were found to reoxidize DNA-bound iron(II), the present results suggest that nitroxides protect by oxidizing reduced transitional metals, thus interfering with the Fenton reaction.
IT **2226-96-2**, **Tempol 2564-83-2**, Tempo
14691-88-4

RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(hydrogen peroxide toxicity to Escherichia coli response to)

L96 ANSWER 34 OF 36 HCAPLUS COPYRIGHT 2001 ACS
AN 1990:494214 HCAPLUS
DN 113:94214
TI Superoxide reaction with nitroxides
AU Samuni, Amram; Krishna, C. Murali; **Mitchell, James B.**; Collins, Christi R.; **Russo, Angelo**
CS Div. Cancer Treat., NCI, Bethesda, MD, 20892, USA
SO Free Radical Res. Commun. (**1990**), 9(3-6), 241-9
CODEN: FRRCEX; ISSN: 8755-0199
DT Journal
LA English
AB Stable, free radical nitroxides are commonly used ESR spectroscopy tools. However, it has recently been found that ESR observable signal from 5-membered ring spin-adducts or stable label nitroxides is lost or diminished by reaction with superoxide. A similar radical-radical annihilation was not found for six-membered ring nitroxide radicals. To discern why six-membered ring nitroxides are not reduced under superoxide flux generated by hypoxanthine/xanthine oxidase, spectrophotometric (Cyt CIII) and chemiluminescence (lucigenin) and ESR assays were used to follow the reactions. Spectrophotometry and chemiluminescence clearly demonstrated that the six-membered piperidine-1-oxyl compds. (TEMPO, TEM-POL, and TEMPAMIN) rapidly react with superoxide: rate consts. at pH 7.8 ranging from 7 .times. 104 to 1.2 .times. 105M-1 s-1. The absence of detectable ESR signal loss results from facile re-oxidn. of the corresponding hydroxylamine by superoxide. To fully corroborate the efficiency of the 6-membered nitroxide superoxide dismutase activity, they were shown to protect fully mammalian cells from oxidative damage resulting from exposure to the superoxide and hydrogen peroxide generating system hypoxanthine/xanthine oxidase. Since six-membered cyclic nitroxides react with superoxide about 2 orders of magnitude faster than the corresponding 5-membered ring nitroxides, they may ultimately be more useful as superoxide dismutase mimetic agents.
IT **2226-96-2**, **TEMPOL 2564-83-2**, TEMPO
14691-88-4
RL: ANST (Analytical study)
(superoxide reaction with)

L96 ANSWER 35 OF 36 HCAPLUS COPYRIGHT 2001 ACS
AN 1987:550397 HCAPLUS
DN 107:150397
TI **Radiosensitizers** and thymine base damage
AU Remsen, Joyce F.
CS Lab. Energy-Relat. Health Res., Univ. California, David, CA, USA
SO NATO ASI Ser., Ser. A (**1986**), 124(Radiat. Carcinog. DNA Alterations), 467-9
CODEN: NALSDJ
DT Journal
LA English
AB The effect of 3 radiosensitizers, misonidazole, p-nitroacetophenone, and 4-**hydroxy**-2,2,6,6-**tetramethylpiperidino**-1-**oxy** (**TMPN**), on formation of thymine damage of the 5,6-dihydroxydihydrothymine type by irradn. with .gamma.-rays was characterized in HeLa cells. The 3 sensitizers have different electron affinities, or, in the case of **TMPN**, are a stable free radical. The formation of thymine base damage was measured in the presence of increasing concns. of each of the 3 sensitizers with and without 500 Gy of 60Co .gamma.-rays, at ice temp. Each sensitizer gave a different result. Increasing concns. of misonidazole suppressed the formation of base damage in air but had no apparent effect under hypoxia. In the presence of p-nitroacetophenone, similar amts. of base damage were formed under both aerobic and hypoxic conditions. **TMPN**, on the other hand, resulted in a complex pattern, with suppression at higher concns. (60 mM).

The overall conclusion is that the sensitizers do not result in increased base damage but, if anything, suppress its formation. Therefore, the mechanism by which they sensitize under hypoxic conditions, such as found in solid **tumors**, is not by an increase in thymine base damage.

IT **2226-96-2**
RL: BIOL (Biological study)
(thymine base damage in DNA of HeLa cells induction by .gamma.-rays response to)

L96 ANSWER 36 OF 36 HCAPLUS COPYRIGHT 2001 ACS
AN 1975:559999 HCAPLUS
DN 83:159999
TI **Radiosensitizing** action in vivo of 2,2,6,6-**tetramethyl**-4-**piperidinol**-N-**oxyl** (**TMPN**)
AU Hill, R. P.; Fielden, E. M.; Lillicrap, S. C.; Stanley, Judith A.
CS Biophys. Dep., Inst. Cancer Res., Sutton, Engl.
SO Int. J. Radiat. Biol. Relat. Stud. Phys., Chem. Med. (**1975**), 27(5), 499-501
CODEN: IJRBA3
DT Journal
LA English
AB No radiosensitizing action of **TMPN** (6 mg, i.p. or i.v. 30 and 10 min before irradn. with 1500-2500 rad) was obsd. in mice bearing B16 melanomas. The rapid fall in **TMPN** concns. in blood, half-life .apprx. 0.5 min., followed by a slow disappearance of **TMPN** probably resulted in failure to observe sensitization.
IT **2226-96-2**
RL: PRP (Properties)
(radiosensitizing effect of, on **melanoma** cells)

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L97 ANSWER 1 OF 20 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:796278 HCAPLUS
TI Synthesis of TEMPO-functionalized G-6-PAMAM(TM)-dendrimers for in vivo EPR imaging.
AU Yordanov, A. T.; Brechbiel, M. W.; Yamada, K.; Krishna, M. C.; **Mitchell, J. B.**
CS Radioimmune and Inorganic Chemistry Section, ROB, DCS, National Cancer Institute, National Institutes of Health, Bethesda, MD, 20892, USA
SO Abstr. Pap. - Am. Chem. Soc. (2000), 220th, MEDI-279
CODEN: ACSRAL; ISSN: 0065-7727
PB American Chemical Society
DT Journal; Meeting Abstract
LA English
AB ESR (EPR) imaging is a promising technique for measuring free radical distribution, metab., and tissue oxygenation in organs and tissues. However, the stable nitroxyl radicals (such as **TEMPOL**, or 4-**hydroxy**-2,2,6,6-**tetramethylpiperidine**-N-**oxyl**) are very prone to in vivo redn. to their hydroxylamine derivs., which are diamagnetic, EPR inactive species. It has been previously reported that the i.v. injection of polynitroxyl-albumin (PNA) causes the re-oxidn. of free (unbound) hydroxylamine back to the paramagnetic nitroxide. Here we report the synthesis and preliminary biol. evaluation of polynitroxyl-G6-PAMAM(TM)-dendrimers, in which TEMPO (2,2,6,6-tetramethyl-1-piperidine-N-oxyl) free radicals were covalently attached to these synthetic spherical macromols. EPR studies on incubations of nitroxide labeled dendrimers with the hydroxylamine 1,4-dihydroxy-2,2,6,6-tetramethylpiperidine provided evidence for electron transfer between the low mol. wt. hydroxylamine and the nitroxide labeled dendrimer. The rate consts. for the electron transfer were evaluated. In vivo EPR studies in mice injected with nitroxide alone, or in presence of dendrimer, were carried out to est. the enhancement of pharmacol. half-life of the low-mol. wt. nitroxide. The studies suggest that nitroxide-labeled

dendrimer could enhance the half-life of **TEMPOL** and that such strategies might be useful in EPR imaging where in the EPR visible form is maintained for longer times.

L97 ANSWER 2 OF 20 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:398057 HCAPLUS
DN 133:159912
TI The pro-oxidative activity of SOD and nitroxide SOD mimics
AU Offer, Tal; **Russo, Angelo**; Samuni, Amram
CS Molecular Biology, Hebrew University - Hadassah Medical School, Jerusalem, 91120, Israel
SO FASEB J. (2000), 14(9), 1215-1223
CODEN: FAJOEC; ISSN: 0892-6638
PB Federation of American Societies for Experimental Biology
DT Journal
LA English
AB Native Cu,Zn-SOD and synthetic SOD mimics sometimes demonstrate an apparently anomalous bell-shaped dose-response relationship when protecting various biol. systems from oxidative stress. Several mechanisms have been proposed to account for such an effect, including: overprodn. of H2O2, peroxidative activity of SOD, and opposing roles played by O2.cntdot.- in both initiation and termination of radical chain reactions. In the present study, ferrocyanide and thiols, which are susceptible to one-electron and two-electron oxidn., resp., were subjected to a flux of superoxide in the presence and absence of SOD or SOD mimics. The results show that 1) either O2.cntdot.-/HO2.cntdot. or H2O2 alone partially inactivates papain, whereas when combined they act synergistically; 2) nitroxide SOD mimics, but not SOD, exhibit a bell-shaped dose-response relationship in protecting papain from inactivation; 3) SOD, which at low dose inhibits superoxide-induced oxidn. of ferrocyanide, loses its antioxidative effect as its concn. increases. These findings offer an addnl. explanation for the pro-oxidative activity of SOD and SOD mimics without invoking any dual activity of O2.cntdot.- or a combined effect of SOD and H2O2. The most significant outcome of an increase in SOD level is a decrease of [O2.cntdot.-]steady state, rather than any notable elevation of [H2O2]steady state. As a result, the reaction kinetics of the high oxidn. state of each catalyst is altered. In the presence of ultra-low [O2.cntdot.-]steady state, the oxidized form of SOD [Cu(II),Zn-SOD] or SOD mimic (oxo ammonium cation) does not react with O2.cntdot.- but rather oxidizes the target mol. that it was supposed to have protected. Consequently, these catalysts exert an anti- or pro-oxidative effect depending on their concn.
RE.CNT 50
RE
(1) Armstrong, D; Photochem Photobiol 1978, V28, P743 HCAPLUS
(2) Beit-Yannai, E; Brain Res 1996, V717, P22 HCAPLUS
(5) Blough, N; Environ Sci Technol 1988, V22, P77 HCAPLUS
(7) Elroy-Stein, O; EMBO J 1986, V5, P615 HCAPLUS
(8) Fridovich, I; Annu Rev Biochem 1995, V64, P97 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L97 ANSWER 3 OF 20 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:318533 HCAPLUS
DN 131:138752
TI Nitroxides as protectors against oxidative stress
AU **Mitchell, James B.**; Krishna, Murali C.; Samuni, Amram; **Russo, Angelo**; Hahn, Stephen M.
CS Radiation Biology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, 20892, USA
SO React. Oxygen Species Biol. Syst. (1999), 293-313. Editor(s): Gilbert, Daniel L.; Colton, Carol A. Publisher: Kluwer Academic/Plenum Publishers, New York, N. Y.
CODEN: 67RAA6
DT Conference; General Review
LA English
AB A review with many refs. of studies evaluating the protective effects of

stable nitroxides in mammalian cells, isolated organs and whole animals subjected to various types of oxidative damage. Nitroxides have been shown to protect biol. systems both in vitro and in vivo by several modes of action and the chem. mechanisms underlying these observations are discussed.

RE.CNT 67

RE

(1) Abe, M; Int J Radiat Oncol Biol Phys 1981, V7, P205 HCAPLUS
(6) Belkin, S; Arch Biochem Biophys 1987, V256, P232 HCAPLUS
(7) Bennett, H; Invest Radiol 1987, V22, P502 HCAPLUS
(8) Bennett, H; Magn Reson Med 1987, V4, P93 HCAPLUS
(12) Chateauneuf, J; J Org Chem 1988, V53, P1629 HCAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L97 ANSWER 4 OF 20 HCAPLUS COPYRIGHT 2001 ACS
AN 1998:160282 HCAPLUS
DN 128:281508
TI The cytotoxicity of nitroxyl: possible implications for the pathophysiological role of NO
AU Wink, David A.; Feelisch, Martin; Fukuto, Jon; Chistodoulou, Danae; Jourd'heuil, David; Grisham, Matthew B.; Vodovotz, Yoram; Cook, John A.; Krishna, Murali; Degraff, William G.; Kim, Sungmee; Gamson, Janet; **Mitchell, James B.**
CS Tumor Biology Section, Radiation Biology Branch, National Cancer Institute, Bethesda, MD, 20892, USA
SO Arch. Biochem. Biophys. (1998), 351(1), 66-74
CODEN: ABBIA4; ISSN: 0003-9861
PB Academic Press
DT Journal
LA English
AB In addn. to the broad repertoire of regulatory functions nitric oxide (NO) serves in mammalian physiol., the L-arginine:NO pathway is also involved in numerous pathophysiol. mechanisms. While NO itself may actually protect cells from the toxicity of reactive oxygen radicals in some cases, it has been suggested that reactive nitrogen oxide species formed from nitric oxide synthase (NOS) can be cytotoxic. In addn. to NO, the one electron redn. product NO- has been proposed to be formed from NOS. The authors investigated the potential cytotoxic role of nitroxyl (NO-), using the nitroxyl donor Angelis's salt, (AS; sodium trioxodinitrate, Na2N2O3) as the source of NO-. AS was cytotoxic to Chinese hamster V79 lung fibroblast cells over a concn. range of 2-4 mM. The presence of equimolar ferricyanide (Fe(III)-(CN6)3-), which converts NO- to NO, afforded dramatic protection against AS-mediated cytotoxicity. Treatment of V79 cells with L-buthionine sulfoximine to reduce intracellular glutathione markedly enhanced AS cytotoxicity, which suggests that GSH is crit. for cellular protection against the toxicity of NO-. Further expts. showed that low mol. wt. transition metal complexes assocd. with the formation of reactive oxygen species are not involved in AS-mediated cytotoxicity since metal chelators had no effect. However, under aerobic conditions, AS was more toxic than under hypoxic conditions, suggesting that oxygen dramatically enhanced AS-mediated cytotoxicity. At a mol. level, AS exposure resulted in DNA double strand breaks in whole cells, and this effect was completely prevented by coincubation of cells with ferricyanide or **Tempol**. The data in this study suggest that nitroxyl may contribute to the cytotoxicity assocd. with an enhanced expression of the L-arginine:NO pathway under different biol. conditions.

L97 ANSWER 5 OF 20 HCAPLUS COPYRIGHT 2001 ACS
AN 1998:104564 HCAPLUS
DN 128:202364
TI Stable free radicals as radiation protectors
AU Hahn, Stephen M.; Krishna, C. Murali; **Mitchell, James B.**
CS USA
SO Radioprotectors (1998), 111-126. Editor(s): Bump, Edward A.; Malaker, Kamal. Publisher: CRC, Boca Raton, Fla.
CODEN: 65PMAI

DT Conference; General Review
LA English
AB A review with 47 refs.

L97 ANSWER 6 OF 20 HCAPLUS COPYRIGHT 2001 ACS
AN 1997:92226 HCAPLUS
DN 126:166187
TI Protection of mitomycin C-induced skin extravasation with the nitroxide, 3-carbamoyl-PROXYL (3-CP)
AU Hahn, Stephen M.; Sullivan, Frank J.; **De Luca, Anne Marie;** Sprague, Merle; Hampshire, Victoria A.; Krishna, Murali C.; **Russo, Angelo; Mitchell, James B.**
CS Radiation Biology Branch, Division of Clinical Sciences, National Cancer Institute, Bethesda, MD, 20892, USA
SO Int. J. Oncol. (**1997**), 10(1), 119-123
CODEN: IJONES; ISSN: 1019-6439
PB International Journal of Oncology
DT Journal
LA English
AB Extravasation tissue injury from chemotherapeutic drugs is a serious clin. problem. A swine model has been useful for studying skin extravasation and evaluating potential antidotes. Mitomycin C (MMC) skin extravasation was studied. Nitroxides, a class of compds. which are protective against a variety of oxidative stresses in vitro, including MMC, were tested as antidotes. Miniature swine were anesthetized and given intradermal (ID) injections of MMC. MMC alone caused skin necrosis and ulceration. Several nitroxides were screened as protectors of MMC-induced skin necrosis. 3-Carbamoyl-PROXYL (3-CP) was the lone nitroxide which protected if given 5 min after extravasation. Administration of 3-CP 10 min after MMC injection was not protective. In vitro studies with monolayered V79 cells showed that 3-CP had a direct protective effect against MMC cytotoxicity in a concn.-dependent fashion. Therefore, in the swine model doses of 3-CP ranging from 25-100 mM were tested and found to protect against MMC skin necrosis 90 days after injection. Histol. sections of the 3-CP- and MMC-treated pig skin showed a marked redn. in the degree of acute inflammation and the absence of deep dermal scarring when compared to MMC alone.

L97 ANSWER 7 OF 20 HCAPLUS COPYRIGHT 2001 ACS
AN 1997:90501 HCAPLUS
DN 126:99335
TI Nitrosylated and nitrated superoxide oxidants and reductants for preventing superoxide-mediated **cell damage** and for treating inflammatory disorders
IN Stamler, Jonathan S.; Crapo, James D.; Fridovich, Irwin; Day, Brian J.; Garvey, David S.
PA Nitromed, Inc., USA; Duke University
SO PCT Int. Appl., 66 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9639409	A1	19961212	WO 1996-US8406	19960603 <--
	W: AU, CA, JP				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9660310	A1	19961224	AU 1996-60310	19960603 <--
PRAI	US 1995-463974		19950605 <--		
	WO 1996-US8406		19960603 <--		

OS MARPAT 126:99335
AB Compds. are provided which comprise a superoxide oxidant or reductant to which is either directly or indirectly linked an NO or NO2 group. More particularly provided are compds. DXR (R = moiety that oxidizes and/or reduces superoxide to oxygen and/or hydrogen peroxide under physiol. conditions; X = S, N, O, C; D = NO, NO2). R can be a functionality contg.

an unpaired electron, a cation (e.g. a physiol. acceptable metal ion), H, or a protective group, or R can be a complex of a transition metal and a macrocyclic ligand that dismutes superoxide under physiol. conditions. These compds. can be used alone or in combination with other therapeutic agents, particularly nitric oxide adducts. Further, the invention provides that the superoxide oxidants or reductants which have not been linked to an NO or NO2 group can be administered in combination or concurrently with nitric oxide or nitric oxide adducts. They are useful for preventing superoxide-mediated **cell damage** and for treating inflammatory disorders in mammals, particularly humans.

L97 ANSWER 8 OF 20 HCAPLUS COPYRIGHT 2001 ACS
AN 1995:979402 HCAPLUS
DN 124:83285
TI **New directions** for free radical **cancer** research and medical applications
AU Hahn, Stephen M.; Krishna, C. Murali; **Mitchell, James B.**
CS National Cancer Institute, National Institutes Health, Bethesda, MD, 20892, USA
SO Adv. Exp. Med. Biol. (**1994**), 366(Free Radicals in Diagnostic Medicine), 241-51
CODEN: AEMBAP; ISSN: 0065-2598
DT Journal; General Review
LA English
AB A review with 36 refs. The development of a class of anti-oxidant compds., the nitroxides, which highlight many of the features of free radicals as they pertain to **cancer** research is described.

L97 ANSWER 9 OF 20 HCAPLUS COPYRIGHT 2001 ACS
AN 1995:791037 HCAPLUS
DN 123:190877
TI Pronounced activation of protein kinase C, ornithine decarboxylase and c-jun proto-oncogene by paraquat-generated active oxygen species in WI-38 human lung cells
AU Kuo, Min-Liang; Lee, Kuen-Chen; Lin, Jen-Kun; Huang, Tze-Sing
CS Institute of Toxicology, college of Medicine National Taiwan University, No. 1, Section 1, Jen-Ai Road, Taipei, Taiwan
SO Biochim. Biophys. Acta (**1995**), 1268(2), 229-36
CODEN: BBACAQ; ISSN: 0006-3002
DT Journal
LA English
AB In this study we examd. the effects of paraquat (Me viologen, PQ) on the protein kinase C (PKC), ornithine decarboxylase (ODC) and c-jun oncogene expression in WI-38 human lung cells. Exposure of cells to 25-200 .mu.M PQ resulted in an increase of [3H]phorbol dibutyrate (PDBu) binding and PKC redistribution in a dose-dependent manner. Interestingly, a superoxide dismutase mimic, 4-hydroxyl-2,2,6,6-tetramethylpiperidine-1-oxyl (**Tempol**, 2.5 mM) and catalase (400 .mu.g/mL) could significantly reduce the PQ-stimulated increase of phorbol ester binding and particular PKC phosphorylating activity, but DMSO (DMSO, 1.5%), an effective .cntdot.OH trapping agent, failed to prevent this stimulation. In addn., an endogenous substrate of PKC, 80 kDa protein, was found to be highly phosphorylated in intact WI-38 cells treated with 50 .mu.M PQ. The increase of phosphorylated proteins could be completely or partly abolished by **Tempol** or catalase, but only the phosphorylation of 80 kDa protein was diminished by protein kinase C inhibitor, 1-(5-isoquinolinylsulfonyl)-2-methylpiperazine (H-7). A maximal peak of ODC activity was obsd. at 6 h of treatment with 50 .mu.M PQ. PQ induced activity was reduced at the following rates, **Tempol** 85%, DMSO 80% and catalase 45%, but H-7 failed to do so. Furthermore, we found that the level of c-jun mRNA was transiently increased by PQ and the peak appeared at 1 h of treatment. When correlated with the PKC result, **Tempol**, catalase and H-7 all effectively blocked PQ-elicited c-jun transcript expression, but DMSO only exhibited a weakly inhibitory effect. We therefore propose that superoxide anion (O2- and H2O2 generated by PQ) could activate PKC and lead to induction of c-jun gene expression; on the

other hand, O2- and .cntdot.OH might trigger other kinase pathways to elevate ODC activity. Finally, the sequential expression of c-jun oncogene and ODC may cooperate to relieve the oxidative damages elicited by PQ.

L97 ANSWER 10 OF 20 HCAPLUS COPYRIGHT 2001 ACS
AN 1994:671515 HCAPLUS
DN 121:271515
TI Free radical modes of cytotoxicity of Adriamycin and streptonigrin
AU DeGraff, William; Hahn, Stephen M.; **Mitchell, J. B.**; Krishna, Murali
CS Radiation Biology Branch, National Inst. of Health, Bethesda, MD, 20892, USA
SO Biochem. Pharmacol. (**1994**), 48(7), 1427-35
CODEN: BCPCA6; ISSN: 0006-2952
DT Journal
LA English
AB Free radical modes of cytotoxicity of streptonigrin (STN) and Adriamycin (ADR) in Chinese hamster V79 cells under aerobic conditions were evaluated using 4-**hydroxy**-2,2,6,6-**tetramethylpiperidine**-1-**oxyl** (TP), a low mol. wt. stable nitroxide free radical with antioxidant properties and desferrioxamine (DF), a transition metal chelator. In addn., exogenous superoxide dismutase (SOD, EC 1.15.1.1) and catalase (CAT, EC1.11.1.6), were tested for cytoprotective effects. EPR studies showed that TP reacts with the semiquinones of both ADR and STN and also with O2- radicals generated during aerobic redox cycling of the resp. semiquinone radicals. Pulsed field gel electrophoresis studies confirmed that DNA double-strand breaks (dsb) induced by STN in V79 cells were inhibited completely by TP, whereas ADR-induced DNA dsb were not affected by TP. Clonogenic cell survival studies showed that STN-induced cytotoxicity could be inhibited completely by DF or TP. Both agents were ineffective in inhibiting ADR-induced cytotoxicity. SOD and CAT were ineffective in protecting against both STN and ADR cytotoxicity. Our results are consistent with a mechanism requiring the semiquinone radical intermediate of STN for cytotoxicity and minimal free radical involvement in ADR-induced V79 cell cytotoxicity.

L97 ANSWER 11 OF 20 HCAPLUS COPYRIGHT 2001 ACS
AN 1994:579003 HCAPLUS
DN 121:179003
TI Novel DMPO-Derived 13C-Labeled Spin Traps Yield Identifiable Stable Nitroxides
AU Barasch, Dinorah; Krishna, Murali C.; **Russo, Angelo**; Katzhendler, Jehoshua; Samuni, Amram
CS School of Medicine and Pharmaceutical Chemistry, Hebrew University, Jerusalem, 91010, Israel
SO J. Am. Chem. Soc. (**1994**), 116(16), 7319-24
CODEN: JACSAT; ISSN: 0002-7863
DT Journal
LA English
AB The nitrone 5,5-dimethyl-1-pyrroline N-oxide (DMPO) is the most common spin trap used for studying free radicals, yet its spin adducts are rapidly and irreversibly destroyed by cells. A Me substitution at the 2-position of DMPO results in the nitrone 2,5,5-trimethyl-1-pyrroline N-oxide (M3PO). Radical addn. to M3PO is expected to produce stable spin adducts; however, they have almost the same N hyperfine splitting (hfs), and, in the absence of a .beta.-hydrogen, different adducts are not distinguishable. To overcome this limitation, the synthesis of M3PO labeled with 13C at the nitronyl (C-2) or the 2-Me (.alpha. or .beta. to the aminoxyl group in the spin adduct, resp.) has been undertaken. [.alpha.-13C]M3PO was synthesized from [2-13C]acetone in a four-step pathway while [.beta.-13C]M3PO was obtained from DMPO and [13C]iodomethane. For M3PO, the nuclear magnetic moment of 13C replaces that of the .beta.-hydrogen of DMPO and provides the addnl. hfs necessary for spin adduct identification. Primary radicals, such as .bul.CH3, .bul.CO2- and .bul.OH were generated radiolytically, sonolytically, or

enzymically, trapped by [13C]M3PO, and gave rise to nitroxide spin adducts which were identified and their magnetic parameters detd. The [13C]M3PO spin adducts were far more stable than those of DMPO. Moreover, they were less susceptible to cellular-induced destruction. However, the superoxide adduct of M3PO was unstable and did not persist.

L97 ANSWER 12 OF 20 HCAPLUS COPYRIGHT 2001 ACS
AN 1994:264641 HCAPLUS
DN 120:264641
TI Potential use of nitroxides in **radiation oncology**
AU Hahn, Stephen M.; Krishna, C. Murali; Samuni, Amram; DeGraff, William; Cuscela, Daniel O.; Johnstone, Peter; **Mitchell, James B.**
CS Radiat. Biol. Sect., Natl. Cancer Inst., Bethesda, MD, 20892, USA
SO Cancer Res. (**1994**), 54(7, Suppl.), 2006s-2010s
CODEN: CNREA8; ISSN: 0008-5472
DT Journal; General Review
LA English
AB A review with 43 refs. The identification of radioprotectors is an important goal for those involved in radiation oncol. and for those interested in the investigation of the mechanisms of radiation cytotoxicity. Recently, a new class of in vitro and in vivo radioprotectors, the nitroxides, has been discovered. The nitroxides are low-mol.-wt. stable free radicals which are freely membrane permeable and which have been shown to act as superoxide dismutase mimics. Further investigation of these compds. has shown that a water-sol. nitroxide, **Tempol**, protects cultured Chinese hamster V79 cells from the cytotoxicity caused by superoxide, hydrogen peroxide, and tert-Bu hydroperoxide. **Tempol** and five other water-sol. nitroxides have also been shown to protect V79 cells against radiation-induced cytotoxicity. Potential mechanisms of protection by the nitroxides include oxidn. of reduced transition metals, superoxide dismutase-like activity, and scavenging of oxy- and carbon-based free radicals. In vivo studies reveal that **Tempol** protects C3H mice from the lethal effects of radiation with a dose causing 50% lethality within 30 days of 9.97 Gy and 7.84 Gy in **Tempol**-treated and saline-treated mice, resp., and a dose modification factor of 1.3. The nitroxides represent a new class of non-thiol radioprotectors which may also have application as general antioxidants. Addnl. work is necessary to screen other nitroxides for in vivo radioprotection and toxicity as well as to fully evaluate the extent to which these compds. protect **tumors**.

L97 ANSWER 13 OF 20 HCAPLUS COPYRIGHT 2001 ACS
AN 1993:663645 HCAPLUS
DN 119:263645
TI Polymerase chain reaction-based deletion screening of bleomycin-induced 6-thioguanine-resistant mutants in Chinese hamster ovary cells: the effects of an inhibitor and a mimic of superoxide dismutase
AU An, Jie; Hsie, Abraham W.
CS Dep. Prev. Med. Community Health, Univ. Texas, Galveston, TX, 77555-1010, USA
SO Mutat. Res. (**1993**), 289(2), 215-22
CODEN: MUREAV; ISSN: 0027-5107
DT Journal
LA English
AB Bleomycin-induced 6-thioguanidine-resistant mutants pretreated with or without TRIEN (triethylenetetramine), a superoxide dismutase (SOD) inhibitor, or **TEMPOL** (4-**hydroxy**-2,2,6,6-**tetramethylpiperidine**-1-**oxyl**), an SOD mimic, were analyzed by polymerase chain reaction (PCR)-based deletion screening in a Chinese hamster ovary (CHO) clone K1-BH4 and its deriv. AS52 cells. As the authors proposed earlier, TRIEN would decrease and **TEMPOL** would increase the intracellular level of hydroxyl radical leading to a higher and lower recovery of deletion mutants. The proportion of the deletion mutants induced by bleomycin at the hypoxanthine-guanine phosphoribosyltransferase (hprt) locus in K1-BH4 cells was 45.5% (25/55). The proportion of deletion HPRT- mutants induced by bleomycin pretreated

with TRIEN was 31.0% (9/29) and with **TEMPOL** was 50.0% (14/28). The proportion of deletion mutants induced by bleomycin on the xanthine-guanine phosphoribosyltransferase (gpt) gene in AS52 cells was 61.0% (36/59). The proportion of deletion GPT- mutants induced by bleomycin pretreated with TRIEN was 56.8% (21/37) and with **TEMPOL** was 61.4% (27/44). The trend of the change of the proportion of bleomycin-induced deletion mutants as affected by TRIEN and by **TEMPOL** provides mol. evidence for the involvement of reactive oxygen species (ROS) in bleomycin mutagenesis in mammalian cells, in which deletion is a major type of induced mutation.

L97 ANSWER 14 OF 20 HCAPLUS COPYRIGHT 2001 ACS
AN 1993:439950 HCAPLUS
DN 119:39950
TI Nitroxyl radicals for **cancer chemotherapy**
AU Emanuel, N. M.; Konovalova, N. P.
CS Inst. Chem. Phys., Moscow, 117977, Russia
SO Bioact. Spin Labels (**1992**), 439-60. Editor(s): Zhdanov, Renat I. Publisher: Springer, Berlin, Germany.
CODEN: 58QYAZ
DT Conference; General Review
LA English
AB A review with 48 refs. The differences in the chemotherapeutic properties of spin-labeled analogs of **antitumor** agents and their parent compds. were proved by a no. of examples. The reasons for these differences are not clear enough yet. Presumably, nitroxyl radicals make cells more sensitive to the damaging action of cytotoxic moiety, as is the case with the effect of radiation, which becomes more pronounced when combined with the action of a nitroxyl radical.

L97 ANSWER 15 OF 20 HCAPLUS COPYRIGHT 2001 ACS
AN 1993:439949 HCAPLUS
DN 119:39949
TI The **toxicity** of aminoxyl radicals
AU Zhdanov, R. I.
CS Inst. Biotechnol., Moscow, 117246, Russia
SO Bioact. Spin Labels (**1992**), 429-38. Editor(s): Zhdanov, Renat I. Publisher: Springer, Berlin, Germany.
CODEN: 58QYAZ
DT Conference; General Review
LA English
AB A review with 63 refs. Heterocyclic aminoxyl (nitroxyl radical possess low hematotoxicity and relatively low acute toxicity. The current literature does not contain data on their chronic toxicity. The toxicity-lowering mechanism by nitroxyl heterocycles as well as their **antitumor** activity seems to be represented by the inhibition of side free-radical reactions and the decrease in the level of toxic metabolites through the capture of free radial intermediates. If this is so, then the application of aminoxyl radicals for preventing the toxic effects of various chems. and drugs would be extremely fruitful. For this point of view, the data on the enhancement of the **antitumor** action of **anticancer** medicines by injection of nitroxyl radicals as well as preventing toxic effects of carbon tetrachlortide are very rewarding. The use of spin traps to prevent the toxic actin of carbon tetrachloride [63] an irradn. also turned out to be very successful. Spin traps may become even more effective than aminoxyl radicals for preventing toxic effects of chems. as they can react with free radical metabolites at least twice.

L97 ANSWER 16 OF 20 HCAPLUS COPYRIGHT 2001 ACS
AN 1990:174935 HCAPLUS
DN 112:174935
TI Diagnostic or radiotherapeutic composition comprising a hydrogen (deuterium)-containing compound
IN Wenzel, Martin
PA Mallinckrodt, Inc., USA; Mallinckrodt Diagnostica (Holland) B. V.

SO PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

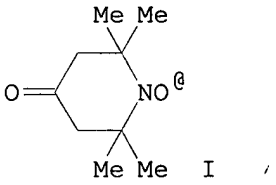
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 8901342	A2	19890223	WO 1988-N	
L33	19880708 <--				
	WO 8901342	A3	19890323		
	W: AU, JP, US				
	RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE				
	AU 8819661	A1	19890309	AU 1988-19661	19880708 <--
	EP 335918	A1	19891011	EP 1988-906139	19880708 <--
	R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
	US 5167948	A	19921201	US 1989-455432	19891121 <--
PRAI	EP 1987-201506	19870807 <--			
	WO 1988-N				
L33	19880708 <--				

OS MARPAT 112:174935
AB Diagnostic or radiotherapeutic compns. comprising a H-contg. compd. [having .gtoreq.1 deuterium (d)] and pharmaceutically acceptable formulation means, etc., have improved target organ specificity. The compns. are used in imaging and controlling or combating **tumors**. A kit for prepg. a radiodiagnostic compn. comprises a nonradiolabeled deuterated compd., and, optionally, a reducing agent, etc. and instructions. Prep. of tert-butylisocyanide-d9 (I) involved reducing tert-butanol-d10 and treating the formamide with diphosgen. I was labeled with 99mTc and the product was compared to the corresponding nondeuterated compd. by administering 1 mL of each i.v. to a baboon. After 60 min the radioactivity in the heart was detd. that for the deuterated compd. was .apprx.7% higher than that for the nondeuterated compd.
IT **7440-54-2D**, Gadolinium, chelates, deuterated
RL: BIOL (Biological study)
(as NMR contrast agents)

L97 ANSWER 17 OF 20 HCAPLUS COPYRIGHT 2001 ACS
AN 1990:135122 HCAPLUS
DN 112:135122
TI Biologically active metal-independent superoxide dismutase mimics
AU **Mitchell, James B.**; Samuni, Amram; Krishna, Murali C.; DeGraff, William G.; Ahn, Min S.; Samuni, Uri; **Russo, Angelo**
CS Div. Cancer Treat., Natl. Cancer Inst., Bethesda, MD, 20892, USA
SO Biochemistry (**1990**), 29(11), 2802-7
CODEN: BICHAW; ISSN: 0006-2960
DT Journal
LA English
AB Attempts to increase intracellular concns. of superoxide dismutase (SOD) by direct application are complicated because SOD, being a relatively large mol., does not readily cross cell membranes. Here, a set of stable nitroxides was identified that possess SOD-like activity, have the advantage of being low-mol.-wt. membrane-permeable, and metal-independent, and at pH 7.0 have reaction rate consts. with superoxide in the range of 1.1 .times. 103-1.3 .times. 106 M-1 s-1. These SOD mimics protect mammalian cells from damage induced by hypoxanthine/xanthine oxidase and H2O2, although they exhibit no catalase-like activity. In addn., the nitroxide SOD mimics rapidly oxidize DNA-Fe (II) and thus may interrupt the Fenton reaction and prevent formation of deleterious OH radicals and/or higher oxidn. states of metal ions. Whether by SOD-like activity and/or interception of an electron from redox-active metal ions they protect cells from oxidative stress and may have use in basic and applied biol. studies.

L97 ANSWER 18 OF 20 HCAPLUS COPYRIGHT 2001 ACS
AN 1983:27421 HCAPLUS
DN 98:27421

TI Influencing the **hepatocarcinogenic** action of diethylnitrosamine by 2,2,6,6-tetramethyl-4-oxopiperidinyl-1-oxy (**TMPO**)
AU Raikov, Z.; Balanski, R.
CS Res. Inst. Oncol., Med. Acad., Sofia, Bulg.
SO Dokl. Bolg. Akad. Nauk (**1982**), 35(7), 1009-11
CODEN: DBANAD; ISSN: 0366-8681
DT Journal
LA English
GI



I

AB The joint treatment of rats with diethylnitrosamine (DENA) [55-18-5] and 2,2,6,6-tetramethyl-4-oxopiperidinyl-1-oxy (I) [**2896-70-0**] led to a certain inhibition of **hepatocarcinogenesis**. The 2-fold administration of I 5 min before DENA and 30 min after, created conditions for the inhibition of certain processes connected with the initiation of the **neoplasms**. The participation of cytochrome P 450 in the oxidative-redn. changes of I and the oxidn. of the .alpha.-C atom of DENA as the 1st stage in the activation of DENA by the same enzyme, may be taken into account in explaining the inhibiting action of I on the **hepatocarcinogenesis** with DENA.
IT **2896-70-0**
RL: BIOL (Biological study)
(diethylnitrosamine-induced liver **neoplasm** inhibition by)

L97 ANSWER 19 OF 20 HCAPLUS COPYRIGHT 2001 ACS
AN 1982:519982 HCAPLUS
DN 97:119982
TI Application of nitroxide free radicals in **cancer chemotherapy**
AU Subczynski, Witold K.
CS Inst. Biol. Mol., Uniw. Jagiellonski, Krakow, 31-001, Pol.
SO Zesz. Nauk. Uniw. Jagiellon., Pr. Biol. Mol. (**1981**), 8, 231-7
CODEN: ZNUMDV
DT Journal; General Review
LA Polish
AB A review with 18 refs.

L97 ANSWER 20 OF 20 HCAPLUS COPYRIGHT 2001 ACS
AN 1977:462729 HCAPLUS
DN 87:62729
TI Improved effectiveness of **tumor irradiation** using the nitroxyl free radical
AU Voronina, S. S.; Pelevina, I. I.
CS Inst. Khim. Fiz., Moscow, USSR
SO Med. Radiol. (**1977**), 22(5), 34-40
CODEN: MERAA9
DT Journal
LA Russian
AB The nitroxyl stable free radical triacetonamine N-oxyl [**2896-70-0**] injected i.p. into mice with solid NKLy **tumors** at 180 mg/kg or with ascites **tumors** at 350 mg/kg 15 min before single or fractionated irradn. increased the **antitumor** effectiveness of the radiation. However,r the potentiating effect of the radical during fractionated irradn. decreased with an increase in the no. of fractions.
IT **2896-70-0**

RL: BIOL (Biological study)
(radiosensitization by)

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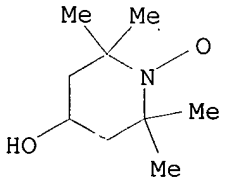
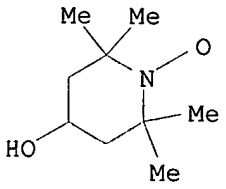
L18 ANSWER 1 OF 2 HCAOLD COPYRIGHT 2001 ACS
AN CA64:2394c CAOLD
TI connection between radiation-protective and **antitumor** action of antioxidants
AU Burlakova, E. B.; Gaintseva, V. D.; Slepukhina, L. V.; Khrapova, N. G.; Emanuel, N. M.
IT 1025-73-6 1123-65-5 1214-63-7 2226-92-8 **2226-96-2**
2226-97-3 2226-98-4 90642-88-9
IT **2226-96-2**
RN 2226-96-2 HCAOLD
CN 1-Piperidinyloxy, 4-hydroxy-2,2,6,6-tetramethyl- (9CI) (CA INDEX NAME)



L18 ANSWER 2 OF 2 HCAOLD COPYRIGHT 2001 ACS
AN CA61:13775a CAOLD
TI **antitumor** activity of stable free radicals
AU Konovalova, N. P.; Bogdanov, G. N.; Miller, V. B.; Neiman, M. B.; Rozantsev, E. G.; Emanuel, N. M.
IT **2226-96-2**
IT **2226-96-2**
RN 2226-96-2 HCAOLD
CN 1-Piperidinyloxy, 4-hydroxy-2,2,6,6-tetramethyl- (9CI) (CA INDEX NAME)



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L113 ANSWER 1 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1997:231500 BIOSIS
DN PREV199799530703
TI DNA damage and apoptosis in human **leukemic** cells treated with the piperidine nitroxide **TEMPOL**.
AU Monti, E. (1); Gariboldi, M. B.; Supino, R.; Piccinini, F.
CS (1) Inst. Pharmacology, Univ. Milan, Milan Italy
SO Proceedings of the American Association for Cancer Research Annual Meeting, (1997) Vol. 38, No. 0, pp. 193.
Meeting Info.: Eighty-eighth Annual Meeting of the American Association for Cancer Research San Diego, California, USA April 12-16, 1997
ISSN: 0197-016X.
DT Conference; Abstract
LA English
CC General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520
Cytology and Cytochemistry - Human *02508
Genetics and Cytogenetics - Human *03508
Pathology, General and Miscellaneous - Necrosis *12510
Pathology, General and Miscellaneous - Therapy *12512
Pharmacology - Clinical Pharmacology *22005
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
BC Hominidae *86215
IT Major Concepts
Cell Biology; Genetics; Oncology (Human Medicine, Medical Sciences); Pathology; Pharmacology
IT Chemicals & Biochemicals
PIPERIDINE NITROXIDE; 4-HYDROXY-2,2,6,6-TETRAMETHYLPIPERIDINE-N-OXYL
IT Miscellaneous Descriptors
ANTINEOPLASTIC-DRUG; APOPTOSIS; BLOOD AND LYMPHATIC DISEASE; CELL CYCLE; CYTOTOXICITY; DNA DAMAGE; DNA FRAGMENTATION; LEUKEMIA; NEOPLASTIC DISEASE; PHARMACOLOGY; PIPERIDINE NITROXIDE; TUMOR BIOLOGY; 4-HYDROXY-2,2,6,6-TETRAMETHYLPIPERIDINE-N-OXYL
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name

HL-60 (Hominidae): cell line; KG-1 (Hominidae): cell line
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates
RN 6146-40-3 (PIPERIDINE NITROXIDE)
2226-96-2 (4-HYDROXY-2,2,6,6-TETRAMETHYLPIPERIDINE-N-OXYL)

L113 ANSWER 2 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1997:216337 BIOSIS
DN PREV199799522841
TI Evaluation of **Tempol** radioprotection in a murine tumor model.
AU Hahn, Stephen M.; Sullivan, Francis J.; **Deluca, Anne Marie;** Krishna, C. Murali; Wersto, Nancy; Venzon, David; **Russo, Angelo; Mitchell, James B. (1)**
CS (1) Radiation Biol. Branch, Natl. Cancer Inst., 9000 Rockville Pike, Build. 10, Room B3B69, Bethesda, MD 20892 USA
SO Free Radical Biology & Medicine, (1997) Vol. 22, No. 7, pp. 1211-1216. ISSN: 0891-5849.
DT Article
LA English
AB **Tempol**, a stable nitroxide free radical compound, is an in vitro and in vivo radioprotector. Previous studies have shown that **Tempol** protects C3H mice against whole-body radiation-induced bone marrow failure. In this study, the radioprotection of tumor tissue was evaluated. RIF-1 tumor cells were implanted in female C3H mice 10 d prior to radiation. Groups of mice were injected intraperitoneally with **Tempol** (275 mg/kg) or PBS followed 10 min later by a single dose of radiation to the tumor bed. Tumor growth curves generated after 10 and 33.3 Gy doses of radiation showed no difference in growth between the **Tempol**- and PBS-treated animals. A full radiation dose-response experiment revealed a tumor control dose in 50% of the animals in 30 d (TCD-50/30) value of 36.7 Gy for **Tempol**-treated mice and 41.8 Gy for saline-treated mice suggesting no protection of the RIF-1 tumor by **Tempol**. Tumor pharmacokinetics were done to determine why **Tempol** differentially protected bone marrow and not tumor cells. Differential reduction of **Tempol** in the RIF-1 tumor and bone marrow was evaluated with EPR spectroscopy 10, 20, and 30 min after injection. Bioreduction of **Tempol** to its corresponding hydroxylamine (which is not a radioprotector) occurred to a greater extent in RIF-1 tumor cells compared to bone marrow. We conclude that the differences in radioprotection may result from enhanced intratumor bioreduction of **Tempol** to its nonradioprotective hydroxylamine analogue. The nitroxides as a class of compounds may provide a means to exploit the redox differences between normal tissues and tumors.
CC Radiation - Radiation Effects and Protective Measures *06506
Biochemical Studies - General *10060
Blood, Blood-Forming Organs and Body Fluids - Blood Cell Studies *15004
Blood, Blood-Forming Organs and Body Fluids - Lymphatic Tissue and Reticuloendothelial System *15008
Pharmacology - General *22002
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Neoplasms and Neoplastic Agents - Pathology; Clinical Aspects; Systemic Effects *24004
BC Muridae *86375
IT Major Concepts
Biochemistry and Molecular Biophysics; Blood and Lymphatics (Transport and Circulation); Pharmacology; Radiation Biology; Tumor Biology
IT Chemicals & Biochemicals
TEMPOL; NITROXIDE; 4-HYDROXY-2,2,6,6-TETRAMETHYLPIPERIDINE-N-OXYL
IT Miscellaneous Descriptors
ANIMAL MODEL; BLOOD AND LYMPHATICS; BONE MARROW; CANCER; C3H; FEMALE; NEOPLASTIC DISEASE; PHARMACOKINETICS; PHARMACOLOGY; RADIOPROTECTION; RADIOPROTECTORANT; RADIOSENSITIVITY; REGROWTH; RIF-1 CELL LINE; STABLE NITROXIDE FREE RADICAL COMPOUND; **TEMPOL**; TRANSPLANTATION; TUMOR BIOLOGY; 4-HYDROXY-2,2,6,6-TETRAMETHYLPIPERIDINE-N-OXYL
ORGN Super Taxa

Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
mouse (Muridae)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman mammals; nonhuman vertebrates; rodents; vertebrates
RN **2226-96-2** (**TEMPOL**)
13408-29-2 (NITROXIDE)
2226-96-2 (4-HYDROXY-2,2,6,6-TETRAMETHYLPIPERIDINE-N-OXYL)

L113 ANSWER 3 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1996:110379 BIOSIS
DN PREV199698682514
TI Nitroxide radicals, modificators of toxic action of **cytostatics**.
AU Konovalova, N. P.
CS Inst. Chem. Phys., Russ. Acad. Sci., Chernogolovka Russia
SO Voprosy Onkologii (St. Petersburg), (1995) Vol. 41, No. 2, pp. 49-50.
ISSN: 0507-3758.
DT Article
LA Russian
CC Biochemical Studies - General *10060
Enzymes - General and Comparative Studies; Coenzymes *10802
Pathology, General and Miscellaneous - Therapy *12512
Digestive System - General; Methods *14001
Pharmacology - General *22002
Toxicology - General; Methods and Experimental *22501
Neoplasms and Neoplastic Agents - General *24002
BC Muridae *86375
IT Major Concepts
Biochemistry and Molecular Biophysics; Digestive System (Ingestion and Assimilation); Enzymology (Biochemistry and Molecular Biophysics); Pathology; Pharmacology; Toxicology; Tumor Biology
IT Chemicals & Biochemicals
NITROXIDE; **TEMPOL**; CYCLOPHOSPHAMIDE; THIOTEPA; 6-MERCAPTOPURINE; CYTOCHROME P-450; NITROXYL
IT Miscellaneous Descriptors
CYCLOPHOSPHAMIDE; LIVER CYTOCHROME P-450; NITROXYL RADICAL; NOTE; **TEMPOL**; THIOTEPA; 6-MERCAPTOPURINE
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
rat (Muridae)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman mammals; nonhuman vertebrates; rodents; vertebrates
RN 13408-29-2 (NITROXIDE)
2226-96-2 (**TEMPOL**)
50-18-0 (CYCLOPHOSPHAMIDE)
52-24-4 (THIOTEPA)
50-44-2 (6-MERCAPTOPURINE)
9035-51-2 (CYTOCHROME P-450)
14332-28-6 (NITROXYL)

L113 ANSWER 4 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1995:186488 BIOSIS
DN PREV199598200788
TI Cytotoxicity of **Tempol**, a piperidine nitroxide spin label, against different **neoplastic** and non-**neoplastic** cell lines.
AU Monti, Elena (1); Gariboldi, Marzia (1); Supino, Rosanna; Piccinini, Francesco (1)
CS (1) Inst. Pharmacol., Univ. Milan, Milan Italy
SO Proceedings of the American Association for Cancer Research Annual Meeting, (1995) Vol. 36, No. 0, pp. 387.
Meeting Info.: Eighty-sixth Annual Meeting of the American Association for Cancer Research Toronto, Ontario, Canada March 18-22, 1995

ISSN: 0197-016X.
DT Conference
LA English
CC General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520
Cytology and Cytochemistry - Animal *02506
Cytology and Cytochemistry - Human *02508
Biochemical Studies - General 10060
Pathology, General and Miscellaneous - Therapy *12512
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
In Vitro Studies, Cellular and Subcellular *32600
BC Hominidae 86215
Rodentia - Unspecified *86265
IT Major Concepts
Cell Biology; Oncology (Human Medicine, Medical Sciences); Pathology; Pharmacology
IT Chemicals & Biochemicals
TEMPOL; PIPERIDINE NITROXIDE
IT Miscellaneous Descriptors
ANTINEOPLASTIC-DRUG; CELL CYCLE EFFECTS; EXPERIMENTAL THERAPEUTICS; MEETING ABSTRACT; PHARMACOKINETICS; RODENT CELL LINES; **TEMPOL**
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia; Rodentia - Unspecified: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae); Rodentia (Rodentia - Unspecified)
ORGN Organism Superterms
animals; chordates; humans; mammals; nonhuman mammals; nonhuman vertebrates; primates; rodents; vertebrates
RN **2226-96-2** (**TEMPOL**)
6146-40-3 (PIPERIDINE NITROXIDE)

L113 ANSWER 5 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1994:474548 BIOSIS
DN PREV199497487548
TI Novel radiation protectors.
AU **Mitchell, James B. (1)**; Hahn, Stephen (1); Liebmann, James (1); Cook, John (1); Krishna, Murali (1); **Russo, Angelo (1)**; Wink, David
CS (1) Radiation Biol. Branch, Natl. Cancer Inst., Bethesda, MD 20892 USA
SO International Journal of Radiation Oncology Biology Physics, (1994) Vol. 30, No. SUPPL. 1, pp. 101.
Meeting Info.: 36th Annual Meeting of the American Society for Therapeutic Radiology and Oncology San Francisco, California, USA October 2-6, 1994
ISSN: 0360-3016.
DT **Conference**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Radiation - Radiation and Isotope Techniques *06504
Biochemical Studies - General 10060
Pathology, General and Miscellaneous - Therapy 12512
Pharmacology - Clinical Pharmacology 22005
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
BC Cricetidae 86310
Muridae *86375
IT Major Concepts
Radiology (Medical Sciences); Tumor Biology
IT Chemicals & Biochemicals
TEMPOL; NITRIC OXIDE
IT Miscellaneous Descriptors
CYTOTOXICITY; MEETING ABSTRACT; NITRIC OXIDE; PHARMACOLOGIC POTENTIAL; RADIOSENSITIZER-DRUG; **TEMPOL**; TUMOR SENSITIZATION

ORGN Super Taxa
Cricetidae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia;
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
hamster (Cricetidae); mouse (Muridae)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman mammals; nonhuman vertebrates;
rodents; vertebrates
RN **2226-96-2 (TEMPOL)**
10102-43-9 (NITRIC OXIDE)

L113 ANSWER 6 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1994:291544 BIOSIS
DN PREV199497304544
TI Protection against hypoxia-mediated SR-4233 cytotoxicity by the stable nitroxide free radical **Tempol**.
AU Herscher, L. L. (1); Krishna, C. M.; Degraff, W.; **Mitchell, J. B.**; **Russo, A.**
CS (1) Radiat. Oncol. Branch, Natl. Cancer Inst., Bethesda, MD 20892 USA
SO Proceedings of the American Association for Cancer Research Annual Meeting, (1994) Vol. 35, No. 0, pp. 634.
Meeting Info.: 85th Annual Meeting of the American Association for Cancer Research San Francisco, California, USA April 10-13, 1994
ISSN: 0197-016X.
DT **Conference**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Cytology and Cytochemistry - Animal 02506
Radiation - Radiation and Isotope Techniques 06504
Radiation - Radiation Effects and Protective Measures *06506
Biochemistry - Gases *10012
Biochemical Studies - General 10060
Pathology, General and Miscellaneous - Therapy 12512
Pharmacology - General *22002
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Neoplasms and Neoplastic Agents - Pathology; Clinical Aspects; Systemic Effects *24004
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
BC Mammalia - Unspecified *85700
IT Major Concepts
Biochemistry and Molecular Biophysics; Pharmacology; Radiation Biology; Tumor Biology
IT Chemicals & Biochemicals
SR-4233; NITROXIDE; **TEMPOL**
IT Miscellaneous Descriptors
ANTINEOPLASTIC-DRUG; MEETING ABSTRACT; METABOLIC-DRUG; RADIATION ONCOLOGY; SR-4233; **TEMPOL**
ORGN Super Taxa
Mammalia - Unspecified: Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
mammal (Mammalia - Unspecified); Mammalia (Mammalia - Unspecified)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman mammals; nonhuman vertebrates; vertebrates
RN 27314-97-2 (SR-4233)
13408-29-2 (NITROXIDE)
2226-96-2 (TEMPOL)

L113 ANSWER 7 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1994:229133 BIOSIS
DN PREV199497242133
TI Potential use of nitroxides in radiation oncology.
AU Hahn, Stephen M. (1); Krishna, C. Murali; Samuni, Amram; Degraff, William; Cuscela, Daniel O.; Johnstone, Peter; **Mitchell, James B.**

CS (1) Radiation Oncology Branch, Natl. Cancer Inst., 9000 Rockville Pike, Building 10, Room B3B69, Bethesda, MD 20892 USA
SO Cancer Research, (1994) Vol. 54, No. 7 SUPPL., pp. 2006S-2010S. ISSN: 0008-5472.
DT General Review
LA English
AB The identification of radioprotectors is an important goal for those involved in radiation oncology and for those interested in the investigation of the mechanisms of radiation cytotoxicity. Recently, a new class of in vitro and in vivo radioprotectors, the nitroxides, has been discovered. The nitroxides are low-molecular-weight stable free radicals which are freely membrane permeable and which have been shown to act as superoxide dismutase mimics. Further investigation of these compounds has shown that a water-soluble nitroxide, **Tempol**, protects cultured Chinese hamster V79 cells from the cytotoxicity caused by superoxide, hydrogen peroxide, and t-butyl hydroperoxide. **Tempol** and rive other water-soluble nitroxides have also been shown to protect V79 cells against radiation-induced cytotoxicity. Potential mechanisms of protection by the nitroxides include oxidation of reduced transition metals, superoxide dismutase-like activity, and scavenging of oxy- and carbon-based free radicals. In vivo studies reveal that **Tempol** protects C3H mice from the lethal effects of radiation with a dose causing 50% lethality within 30 days of 9.97 Gy and 7.84 Gy in **Tempol** -treated and saline-treated mice, respectively, and a dose modification factor of 1.3. The nitroxides represent a new class of non-thiol radioprotectors which may also have application as general antioxidants. Additional work is necessary to screen other nitroxides for in vivo radioprotection and toxicity as well as to fully evaluate the extent to which these compounds protect tumors.
CC Radiation - Radiation and Isotope Techniques *06504
Radiation - Radiation Effects and Protective Measures *06506
Biochemical Studies - General 10060
Pathology, General and Miscellaneous - Therapy 12512
Pharmacology - General *22002
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
BC Muridae *86375
IT Major Concepts
Pharmacology; Radiation Biology; Radiology (Medical Sciences); Tumor Biology
IT Chemicals & Biochemicals
NITROXIDES; **TEMPOL**
IT Miscellaneous Descriptors
RADIOPROTECTORANT-DRUG; **TEMPOL**; TUMOR TREATMENT
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
mouse (Muridae)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman mammals; nonhuman vertebrates; rodents; vertebrates
RN 13408-29-2D (NITROXIDES)
2226-96-2 (TEMPOL)

L113 ANSWER 8 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1993:517802 BIOSIS
DN PREV199345116427
TI Protection from radiation-induced alopecia with topical application of nitroxides: Fractionated studies.
AU Cuscela, Daniel; Coffin, Deborah; Muldoon, Rebecca; Glass, Joe; Krishna, Murali C.; Bernstein, Eric; **Mitchell, James B.**
CS Radiation Biol. Sect., Radiation Oncology Branch, Natl. Cancer Inst., Natl. Inst. Health, Bethesda, MD USA
SO International Journal of Radiation Oncology Biology Physics, (1993) Vol. 27, No. SUPPL. 1, pp. 197.
Meeting Info.: 35th Annual Meeting of the American Society for Therapeutic

Radiology and Oncology New Orleans, Louisiana, USA October 11-15, 1993
ISSN: 0360-3016.
DT **Conference**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Radiation - Radiation and Isotope Techniques *06504
Radiation - Radiation Effects and Protective Measures *06506
Biochemical Studies - General 10060
Chordate Body Regions - Head 11304
Pathology, General and Miscellaneous - Therapy 12512
Integumentary System - General; Methods 18501
Integumentary System - Pathology *18506
Pharmacology - Clinical Pharmacology *22005
Pharmacology - Integumentary System, Dental and Oral Biology *22020
Routes of Immunization, Infection and Therapy 22100
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
BC Hominidae 86215
Caviidae *86300
IT Major Concepts
Dermatology (Human Medicine, Medical Sciences); Oncology (Human Medicine, Medical Sciences); Pharmacology; Radiation Biology; Radiology (Medical Sciences)
IT Chemicals & Biochemicals
NITROXIDES; **TEMPOL**
IT Miscellaneous Descriptors
ABSTRACT; CANCER TREATMENT; DERMATOLOGICAL-DRUG; GUINEA-PIG; RADIOPROTECTORANT-DRUG; TEMPO; **TEMPOL**
ORGN Super Taxa
Caviidae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia; Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae); Caviidae (Caviidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; nonhuman mammals; nonhuman vertebrates; primates; rodents; vertebrates
RN 13408-29-2D (NITROXIDES)
2226-96-2 (TEMPOL)

L113 ANSWER 9 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1993:400462 BIOSIS
DN PREV199345059287
TI The radioprotector **tempol** does not decrease radiation-induced RIF tumor control in C3H mice.
AU Hahn, S. M.; Sullivan, F.; **Deluca, A. M.**; Krishna, M. C.; Glass, J.; **Russo, A.**; **Mitchell, J. B.**
CS Radiation Oncology Branch, NCI, NIH, Bethesda, MD USA
SO Proceedings of the American Association for Cancer Research Annual Meeting, (1993) Vol. 34, No. 0, pp. 433.
Meeting Info.: 84th Annual Meeting of the American Association for Cancer Research Orlando, Florida, USA May 19-22, 1993
ISSN: 0197-016X.
DT **Conference**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Radiation - Radiation Effects and Protective Measures *06506
Biochemical Studies - General *10060
Pathology, General and Miscellaneous - Therapy *12512
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
BC Muridae *86375
IT Major Concepts
Biochemistry and Molecular Biophysics; Pathology; Radiation Biology; Tumor Biology

IT Chemicals & Biochemicals
TEMPOL
IT Miscellaneous Descriptors
ABSTRACT; ANTIOXIDANT; RADIOPROTECTORANT; STABLE FREE RADICAL
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
Muridae (Muridae)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman vertebrates; nonhuman mammals; rodents; vertebrates
RN **2226-96-2 (TEMPOL)**

L113 ANSWER 10 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1993:400461 BIOSIS
DN PREV199345059286
TI Stem cell factor (SCF) and **tempol** act in synergy to protect mice from lethal irradiation.
AU Liebmann, J. (1); **Deluca, A. M. (1)**; Epstein, A. (1); Steinberg, S.; **Russo, A. (1)**; **Mitchell, J. B. (1)**
CS (1) Radiation Oncology Branch, NCI, NIH, Bethesda, MD USA
SO Proceedings of the American Association for Cancer Research Annual Meeting, (1993) Vol. 34, No. 0, pp. 433.
Meeting Info.: 84th Annual Meeting of the American Association for Cancer Research Orlando, Florida, USA May 19-22, 1993
ISSN: 0197-016X.
DT **Conference**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Cytology and Cytochemistry - Animal *02506
Radiation - Radiation Effects and Protective Measures *06506
Biochemical Studies - General *10060
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Blood, Blood-Forming Organs and Body Fluids - Lymphatic Tissue and Reticuloendothelial System 15008
Endocrine System - General *17002
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
BC Muridae *86375
IT Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology; Endocrine System (Chemical Coordination and Homeostasis); Radiation Biology; Tumor Biology
IT Chemicals & Biochemicals
TEMPOL
IT Miscellaneous Descriptors
ABSTRACT; CANCER RADIOTHERAPY; RADIOPROTECTORANT; STABLE FREE RADICAL
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
Muridae (Muridae)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman vertebrates; nonhuman mammals; rodents; vertebrates
RN **2226-96-2 (TEMPOL)**

L113 ANSWER 11 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1992:404184 BIOSIS
DN BR43:60059
TI MODULATION OF DOXORUBICIN ADR AND STREPTONIGRIN STN CYTOTOXICITY IN CHINESE HAMSTER V79 CELLS BY A STABLE NITROXIDE FREE RADICAL **TEMPOL** TP.
AU KRISHNA M C; HAHN S M; DE GRAFF W; SAMUNI A; **MITCHELL J B**; **RUSSO A**
CS RADIATION ONCOL. BRANCH, NCI, NIH, BETHESDA, MD.

SO 83RD ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, SAN DIEGO, CALIFORNIA, USA, MAY 20-23, 1992. PROC AM ASSOC CANCER RES ANNU MEET. (1992) 33 (0), 509.
CODEN: PAMREA.
DT **Conference**
FS BR; OLD
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Cytology and Cytochemistry - Animal *02506
Biochemical Studies - General 10060
Enzymes - Physiological Studies *10808
Metabolism - Energy and Respiratory Metabolism *13003
Cardiovascular System - Heart Pathology *14506
Pharmacology - General *22002
Toxicology - Pharmacological Toxicology *22504
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
BC Cricetidae 86310
IT Miscellaneous Descriptors
ABSTRACT ANTINEOPLASTIC-DRUG SUPEROXIDE DISMUTASE CARDIOTOXICITY
RN **2226-96-2** (**TEMPOL**)
3930-19-6 (STREPTONIGRIN)
9054-89-1 (SUPEROXIDE DISMUTASE)
13408-29-2 (NITROXIDE)
23214-92-8 (DOXORUBICIN)

L113 ANSWER 12 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1992:282603 BIOSIS
DN BA94:7253
TI **TEMPOL** A STABLE FREE RADICAL IS A NOVEL MURINE RADIATION PROTECTOR.
AU HAHN S M; TOCHNER Z; KRISHNA C M; GLASS J; WILSON L; SAMUNI A; SPRAGUE M; VENZON D; GLATSTEIN E; **MITCHELL J B; RUSSO A**
CS RADITION ONCOL. BRANCH/NATIONAL CANCER INST., BUILDING 10, ROOM B3-B69, BETHESDA, MD. 20892.
SO CANCER RES, (1992) 52 (7), 1750-1753.
CODEN: CNREA8. ISSN: 0008-5472.
FS BA; OLD
LA English
AB Nitroxide compounds are stable free radicals which were previously investigated as hypoxic cell radiosensitizers. The stable nitroxide 4-hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl (**Tempol**) has recently been shown to protect aerated cells in culture against superoxide generated from hypoxanthine/xanthine oxidase, hydrogen peroxide, and radiation-induced cytotoxicity and to modestly sensitize hypoxic cultured cells. To extend these observations from the cellular level to the whole animal, the toxicity, pharmacology, and in vivo radioprotective effects of **Tempol** were studied in C3H mice. The maximum tolerated dose of **Tempol** administered i.p. was found to be 275 mg/kg, which resulted in maximal **Tempol** levels in whole blood 5-10 min after injection. Mice were exposed to whole-body radiation in the absence or presence of injected **Tempol** (275 mg/kg) 5-10 min after administration. **Tempol** treatment provided significant radioprotection ($P < 0.0001$); the dose of radiation at which 50% of **Tempol**-treated mice die at 30 days was 9.97 Gy, versus 7.84 Gy for control mice. **Tempol** represents a new class of in vivo, non-sulfur-containing radiation protectors. Given the potential for hypoxic radiosensitization and aerobic cell radioprotection, **Tempol** or other analogues may have potential therapeutic application.
CC Cytology and Cytochemistry - Animal *02506
Radiation - Radiation and Isotope Techniques *06504
Radiation - Radiation Effects and Protective Measures *06506
Biochemistry - Gases *10012
Biochemical Studies - General 10060

Biophysics - Molecular Properties and Macromolecules 10506
Enzymes - Physiological Studies 10808
Pathology, General and Miscellaneous - Necrosis 12510
Pathology, General and Miscellaneous - Therapy 12512
Metabolism - General Metabolism; Metabolic Pathways 13002
Metabolism - Energy and Respiratory Metabolism *13003
Pharmacology - General *22002
Routes of Immunization, Infection and Therapy 22100
Toxicology - Pharmacological Toxicology 22504
Neoplasms and Neoplastic Agents - Neoplastic Cell Lines *24005
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
Tissue Culture, Apparatus, Methods and Media 32500
BC Muridae 86375
IT Miscellaneous Descriptors
MOUSE RADIOPROTECTORANT-DRUG HYPOXIC RADIOSENSITIZATION ANTINEOPLASTIC-DRUG
RN **2226-96-2 (TEMPOL)**

L113 ANSWER 13 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1992:275279 BIOSIS
DN BR42:134229
TI TOPICAL APPLICATION OF NITROXIDE PROTECTS RADIATION-INDUCED ALOPECIA IN GUINEA-PIGS.
AU GOFFMAN T; CUSCELA D; GLASS J; HAHN S; KRISHNA C M; LUPTON G; **MITCHELL J B**
CS RADIATION ONCOLOGY BRANCH, NCI, BLDG. 10, B3-B69, 9000 ROCKVILLE PIKE, BETHESDA, MD. 20892.
SO SEVENTH INTERNATIONAL CONFERENCE ON CHEMICAL MODIFIERS OF CANCER TREATMENT, PART 2, CLEARWATER, FLORIDA, USA, FEBRUARY 2-5, 1991. INT J RADIAT ONCOL BIOL PHYS. (1992) 22 (4), 803-806.
CODEN: IOBPD3. ISSN: 0360-3016.
DT **Conference**
FS BR; OLD
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Radiation - Radiation and Isotope Techniques 06504
Radiation - Radiation Effects and Protective Measures *06506
Biochemical Studies - General 10060
Integumentary System - Pathology *18506
Pharmacology - Integumentary System, Dental and Oral Biology *22020
BC Caviidae 86300
IT Miscellaneous Descriptors
TEMPOL RADIOPROTECTORANT-DRUG
RN **2226-96-2 (TEMPOL)**
13408-29-2 (NITROXIDE)

L113 ANSWER 14 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1992:206346 BIOSIS
DN BR42:99421
TI NITROXIDE-MEDIATED PROTECTION AGAINST X-RAY OR NEOCARZINOSTATIN INDUCED MUTAGENICITY AND DNA DAMAGE.
AU DEGRAFF W G; KRISHNA M C; **RUSSO A**; KAUFMAN D; **MITCHELL J B**
CS RADIAT. ONCOL. BRANCH, NATL. CANCER INST., NIH, BETHESDA, MD. 20892.
SO 23RD ANNUAL SCIENTIFIC MEETING OF THE ENVIRONMENTAL MUTAGEN SOCIETY, RENO/SPARKS, NEVADA, USA, MARCH 15-19, 1992. ENVIRON MOL MUTAGEN SUPPL. (1992) 0 (20), 14.
CODEN: EMMSEA.
DT **Conference**
FS BR; OLD
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Genetics and Cytogenetics - Animal *03506

Radiation - General *06502
Radiation - Radiation Effects and Protective Measures *06506
Biochemical Studies - General 10060
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines *10062
Biophysics - Molecular Properties and Macromolecules *10506
Pathology, General and Miscellaneous - Therapy *12512
Metabolism - Nucleic Acids, Purines and Pyrimidines *13014
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
In Vitro Studies, Cellular and Subcellular *32600
BC Cricetidae 86310
IT Miscellaneous Descriptors
ABSTRACT CHINESE HAMSTER CHO AS52 CELLS 4 HYDROXY-2 2 6 6-TETRAMETHYLPIPERIDINYLOXYL **TEMPOL** RADIOPROTECTORANT-DRUG SCAVENGER FREE RADICAL
RN **2226-96-2** (**TEMPOL**)
9014-02-2 (NEOCARZINOSTATIN)
13408-29-2 (NITROXIDE)

L113 ANSWER 15 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1992:98575 BIOSIS
DN BA93:55125
TI MECHANISMS OF HYPOXIC AND AEROBIC CYTOTOXICITY OF MITOMYCIN C IN CHINESE HAMSTER V79 CELLS.
AU KRISHNA M C; DEGRAFF W; TAMURA S; GONZALEZ F J; SAMUNI A; **RUSSO A** ; **MITCHELL J B**
CS RADIATION ONCOLOGY BRANCH, CLINICAL ONCOLOGY PROGRAM, NATIONAL CANCER INST., NIH, BETHESDA, MARYLAND 20892, USA.
SO CANCER RES, (1991) 51 (24), 6622-6628.
CODEN: CNREA8. ISSN: 0008-5472.
FS BA; OLD
LA English
AB Mitomycin C (MMC) induced aerobic and hypoxic cytotoxicity in Chinese hamster V79 cells was studied to evaluate the role of the 1-electron versus 2-electron reductive bioactivation. Superoxide dismutase, catalase, and desferal had no protective effects on the aerobic or hypoxic cytotoxicity of MMC, whereas **Tempol** and **Tempol**-H, which are known to interrupt and terminate radical reactions, provided partial protection under aerobic conditions. However, under hypoxic conditions, **Tempol** provided complete protection whereas **Tempol**-H was ineffective. Electron paramagnetic resonance and spin-trapping investigations, designed to study the mechanisms of such protective effects, confirmed that MMC is activated by the human NADPH:cytochrome P-450 oxidoreductase to its semiquinone radical and that, under aerobic conditions, the semiquinone of MMC reduces H2O2 to produce OH radicals as detected by electron paramagnetic resonance-spin trapping with 5,5-dimethyl-1-pyrroline N-oxide. The 1-electron reduced product of MMC was also found of **Tempol**-H by MMC-. was negligible. Cell survival studies and electron paramagnetic resonance observations indicate that the hypoxic cytotoxicity of MMC is mediated by 1-electron activation to its semiquinone intermediate. Under aerobic conditions, the steady state concentration of this intermediate is low due to the facile autooxidation of the semiquinone producing O2-. and H2O2 which are capable of causing oxidative cytotoxicity. **Tempol**, which can accept an electron from reducing radical species, completely inhibited the hypoxic cytotoxicity of MMC indicating MMC-., the semiquinone of MMC as the species responsible for DNA alkylation and selective hypoxic cytotoxicity of MMC. Our results also indicate that the aerobic cytotoxicity is mediated by other processes in addition to the 1-electron mediated activation.
CC Cytology and Cytochemistry - Animal *02506
Biochemical Studies - General 10060
Biophysics - Molecular Properties and Macromolecules 10506
Enzymes - Physiological Studies *10808
Pathology, General and Miscellaneous - Therapy 12512
Metabolism - General Metabolism; Metabolic Pathways *13002
Metabolism - Energy and Respiratory Metabolism *13003

Metabolism - Nucleic Acids, Purines and Pyrimidines *13014
Pharmacology - General *22002
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Pharmacology - Clinical Pharmacology 22005
Neoplasms and Neoplastic Agents - Neoplastic Cell Lines *24005
Neoplasms and Neoplastic Agents - Biochemistry *24006
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
Tissue Culture, Apparatus, Methods and Media 32500
BC Hominidae 86215
Cricetidae 86310
IT Miscellaneous Descriptors
HUMAN ANTINEOPLASTIC-DRUG ELECTRON ACTIVATION NADPH CYTOCHROME P-450 OXIDOREDUCTASE HYDROGEN PEROXIDE REDUCTION HYDROXYL RADICAL PRODUCTION DNA ALKYLATION
RN 50-07-7 (MITOMYCIN C)
7722-84-1 (HYDROGEN PEROXIDE)

L113 ANSWER 16 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1991:107182 BIOSIS
DN BR40:50002
TI PROTECTION AGAINST MITOMYCIN C INDUCED CYTOTOXICITY BY THE STABLE NITROXIDE RADICAL **TEMPOL**.
AU **MITCHELL J B**; DEGRAFF W; KRISHNA C M; SAMUNI A; HAHN S; **RUSSO A**
CS RADIATION ONCOL. BRANCH, NATL. CANCER INST., NATL. INST. HEALTH, BESTHESDA, MD. 20892.
SO MEETING ON OXIDATIVE DAMAGE AND REPAIR HELD AT THE 5TH BIENNIAL MEETING OF THE INTERNATIONAL SOCIETY FOR FREE RADICAL RESEARCH, PASADENA, CALIFORNIA, USA, NOVEMBER 14-20, 1990. FREE RADICAL BIOL MED. (1990) 9 (SUPPL 1), 173. CODEN: FRBMEH. ISSN: 0891-5849.
DT **Conference**
FS BR; OLD
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Cytology and Cytochemistry - Animal *02506
Biochemical Studies - General *10060
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines 10062
Biophysics - Molecular Properties and Macromolecules 10506
Enzymes - Physiological Studies *10808
Pharmacology - General *22002
Tissue Culture, Apparatus, Methods and Media 32500
BC Cricetidae 86310
IT Miscellaneous Descriptors
ABSTRACT CHINESE HAMSTER V79 CELLS 4 HYDROXY-2 2 6 6-TETRAMETHYLPIPERIDINOXYL DNA ADP SUPEROXIDE DISMUTASE
RN 50-07-7 (MITOMYCIN C)
2226-96-2 (**TEMPOL**)
2226-96-2 (4 HYDROXY-2 2 6 6-TETRAMETHYLPIPERIDINOXYL)
9054-89-1 (SUPEROXIDE DISMUTASE)
13408-29-2 (NITROXIDE)
58-64-0Q, 7722-76-1Q (ADP)

L113 ANSWER 17 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1991:107174 BIOSIS
DN BR40:49994
TI IN-VITRO-IN-VIVO RADIATION PROTECTION BY NITROXIDE STABLE FREE RADICALS.
AU HAHN S M; WILSON L; TOCHNER Z; KRISHNA C M; SAMUNI A; **MITCHELL J B** ; **RUSSO A**
CS RADIATION ONCOL. BRANCH, NATL. CANCER INST., NATL. INST. HEALTH, BETHESDA, MD. 20892.
SO MEETING ON OXIDATIVE DAMAGE AND REPAIR HELD AT THE 5TH BIENNIAL MEETING OF THE INTERNATIONAL SOCIETY FOR FREE RADICAL RESEARCH, PASADENA, CALIFORNIA, USA, NOVEMBER 14-20, 1990. FREE RADICAL BIOL MED. (1990) 9 (SUPPL 1), 171. CODEN: FRBMEH. ISSN: 0891-5849.

DT **Conference**
FS BR; OLD
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Cytology and Cytochemistry - Animal *02506
Radiation - Radiation and Isotope Techniques *06504
Radiation - Radiation Effects and Protective Measures *06506
Biochemical Studies - General *10060
Enzymes - Physiological Studies *10808
Pathology, General and Miscellaneous - Therapy 12512
Pharmacology - General *22002
Tissue Culture, Apparatus, Methods and Media 32500
In Vitro Studies, Cellular and Subcellular 32600
BC Cricetidae 86310
IT Miscellaneous Descriptors
ABSTRACT CHINESE HAMSTER V79 CELLS 4 HYDROXY-2 2 6 6-TETRAMETHYLPIPERIDINOXYL RADIOPROTECTORANT AGENT
RN **2226-96-2** (4 HYDROXY-2 2 6 6-TETRAMETHYLPIPERIDINOXYL)
13408-29-2 (NITROXIDE)

=> fil cancer

FILE 'CANCERLIT' ENTERED AT 13:43:48 ON 30 JAN 2001

FILE COVERS 1963 TO 28 Nov 2000 (20001128/ED)

CANCERLIT thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2000 vocabulary. Enter HELP THESAURUS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all tot

L125 ANSWER 1 OF 13 CANCERLIT
AN 1998025416 CANCERLIT
DN 98025416
TI **Tempol** inhibits neutrophil and hydrogen peroxide-mediated DNA damage.
AU Hahn S M; Mitchell J B; Shacter E
CS Radiation Biology Branch, National Cancer Institute, Bethesda, MD 20892, USA.
SO FREE RADICAL BIOLOGY AND MEDICINE, **(1997)**. Vol. 23, No. 6, pp. 879-84.
Journal code: FRE. ISSN: 0891-5849.
DT Journal; Article; (JOURNAL ARTICLE)
FS MEDL; L; Priority Journals
LA English
OS MEDLINE 98025416
EM 199712
AB Inflammatory conditions characterized by neutrophil activation are associated with a variety of chronic diseases. Reactive oxygen species are produced by activated neutrophils and produce DNA damage which may lead to tissue damage. Previous studies have shown that activated murine neutrophils induce DNA strand breaks in a target plasmacytoma cell, RIMPC 2394. We studied the effect of a water soluble nitroxide anti-oxidant, **Tempol**, on murine neutrophil induction of DNA strand breaks in this system. Murine neutrophils were isolated from the peritoneal cavity of BALB/cAn mice after an i.p. injection of pristane oil. Neutrophils were activated by the phorbol ester PMA and co-incubated with RIMPC 2394 cells. Control alkaline elution studies revealed progressive DNA strand breaks in RIMPC cells with time. The addition of **Tempol** to the incubation mixture prevented DNA damage in a dose dependent fashion. Five mM

Tempol provided complete protection. **Tempol** protection against DNA strand breaks was similar for both stimulated neutrophils and exogenously added hydrogen peroxide. Measurement of hydrogen peroxide produced by stimulated neutrophils demonstrated that **Tempol** did not decrease hydrogen peroxide concentration. Oxidation of reduced metals, thereby interfering with the production of hydroxyl radical, is the most likely mechanism of nitroxide protection, although superoxide dismutase (SOD) like activity and scavenging of carbon-based free radicals may also account for a portion of the observed protection. The anti-oxidant activity of **Tempol** inhibited DNA damage by activated neutrophils. The nitroxides as a class of compounds may have a role in the investigation and modification of inflammatory conditions.

CT Check Tags: Animal
*Antioxidants: PD, pharmacology
Cells, Cultured
*Cyclic N-Oxides: PD, pharmacology
***DNA Damage: DE, drug effects**
*Hydrogen Peroxide: TO, toxicity
Mice
Mice, Inbred BALB C
Neutrophil Activation: DE, drug effects
*Neutrophils: DE, drug effects
Neutrophils: ME, metabolism
Peritoneal Cavity: CY, cytology
Plasmacytoma
Reactive Oxygen Species: ME, metabolism
Respiratory Burst: DE, drug effects
Tumor Cells, Cultured

RN **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; 7722-84-1 (Hydrogen Peroxide)

CN 0 (Antioxidants); 0 (Cyclic N-Oxides); 0 (Reactive Oxygen Species)

L125 ANSWER 2 OF 13 CANCERLIT

AN 97252526 CANCERLIT

DN 97252526

TI Evaluation of **tempol** radioprotection in a murine tumor model.

AU Hahn S M; Sullivan F J; DeLuca A M; Krishna C M; Wersto N; Venzon D; Russo A; Mitchell J B

CS Radiation Biology Branch, National Cancer Institute, Bethesda, MD 20892, USA.

SO FREE RADICAL BIOLOGY AND MEDICINE, **(1997)**. Vol. 22, No. 7, pp. 1211-6.
Journal code: FRE. ISSN: 0891-5849.

DT Journal; Article; (JOURNAL ARTICLE)

FS MEDL; L; Priority Journals

LA English

OS MEDLINE 97252526

EM 199709

AB **Tempol**, a stable nitroxide free radical compound, is an in vitro and in vivo radioprotector. Previous studies have shown that **Tempol** protects C3H mice against whole-body radiation-induced bone marrow failure. In this study, the radioprotection of tumor tissue was evaluated. RIF-1 tumor cells were implanted in female C3H mice 10 d prior to radiation. Groups of mice were injected intraperitoneally with **Tempol** (275 mg/kg) or PBS followed 10 min later by a single dose of radiation to the tumor bed. Tumor growth curves generated after 10 and 33.3 Gy doses of radiation showed no difference in growth between the **Tempol**- and PBS-treated animals. A full radiation dose-response experiment revealed a tumor control dose in 50% of the animals in 30 d (TCD(50/30)) value of 36.7 Gy for **Tempol**-treated mice and 41.8 Gy for saline-treated mice suggesting no protection of the RIF-1 tumor by **Tempol**. Tumor pharmacokinetics were done to determine why **Tempol** differentially protected bone marrow and not tumor cells. Differential reduction of **Tempol** in the RIF-1 tumor and bone marrow was evaluated with EPR spectroscopy 10, 20, and 30 min after injection. Bioreduction of **Tempol** to its corresponding

hydroxylamine (which is not a radioprotector) occurred to a greater extent in RIF-1 tumor cells compared to bone marrow. We conclude that the differences in radioprotection may result from enhanced intratumor bioreduction of **Tempol** to its nonradioprotective hydroxylamine analogue. The nitroxides as a class of compounds may provide a means to exploit the redox differences between normal tissues and tumors.

CT Check Tags: Animal; Female
Bone Marrow: DE, drug effects
Bone Marrow: RE, radiation effects
Cell Division: DE, drug effects
Cyclic N-Oxides: ME, metabolism
*Cyclic N-Oxides: PD, pharmacology
Cyclic N-Oxides: PK, pharmacokinetics
Electron Spin Resonance Spectroscopy
Mice
Mice, Inbred C3H
Neoplasm Transplantation
Neoplasms, Experimental: ME, metabolism
*Neoplasms, Experimental: PA, pathology
Neoplasms, Experimental: RT, radiotherapy
*Radiation Tolerance: DE, drug effects
*Radiation-Protective Agents: PD, pharmacology
Radiation-Protective Agents: PK, pharmacokinetics

RN **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**

CN 0 (Cyclic N-Oxides); 0 (Radiation-Protective Agents)

L125 ANSWER 3 OF 13 CANCERLIT

AN 97030736 CANCERLIT

DN 97030736

TI Effects of reactive oxygen species (ROS) modulators, **TEMPOL** and catalase, on methoxyacetaldehyde (MALD) -induced chromosome aberrations in Chinese hamster ovary (CHO)-AS52 cells.

AU Ratanavalachai T C; Au W W

CS Department of Biochemistry, Faculty of Medicine, Chiang Mai University, Thailand. mdbci010.chiangmai.ac.th.

NC R01 ES 04926 (NIEHS)

SO MUTATION RESEARCH, **(1996)**. Vol. 357, No. 1-2, pp. 25-33.
Journal code: NNA. ISSN: 0027-5107.

DT Journal; Article; (JOURNAL ARTICLE)

FS MEDL; L; Priority Journals; Cancer Journals

LA English

OS MEDLINE 97030736

EM 199612

AB Methoxyacetaldehyde (MALD), a metabolite of 2-methoxyethanol, has been shown to be clastogenic and mutagenic in CHO-AS52 cells. PCR-based-deletion screening of MALD induced CHO-AS52 mutants indicates that MALD induces large deletion mutation. Since MALD has an aldehyde as its reactive functional group, it can react with aldehyde oxidase to produce superoxide. The generation of these reactive oxygen species (superoxide, hydrogen peroxide and hydroxyl radical) may be the mechanism for genotoxicity of MALD. In the present study, **TEMPOL** and catalase which are ROS modulators were used to study the effects on MALD-induced chromosome damage in CHO-AS52 cells. The results showed that neither **TEMPOL** nor catalase can protect cells from MALD-induced chromosome aberrations. Therefore, the generation of reactive oxygen species may not be the primary mechanism of action of MALD.

CT Check Tags: Animal; Support, U.S. Gov't, P.H.S.
*Acetaldehyde: AA, analogs & derivatives
Acetaldehyde: TO, toxicity
*Catalase: PD, pharmacology
Chromosome Aberrations
*Cyclic N-Oxides: PD, pharmacology
CHO Cells
***DNA Damage: DE, drug effects**
*Free Radical Scavengers: PD, pharmacology
Hamsters

*Reactive Oxygen Species
*Teratogens: PD, pharmacology
Time Factors
RN 10312-83-1 (2-methoxyacetaldehyde); **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; 75-07-0 (Acetaldehyde)
CN EC 1.11.1.6 (Catalase); 0 (Cyclic N-Oxides); 0 (Free Radical Scavengers); 0 (Reactive Oxygen Species); 0 (Teratogens)

L125 ANSWER 4 OF 13 CANCERLIT
AN 96140768 CANCERLIT
DN 96140768
TI Modulation of sensitivity to mitomycin C and a dithiol analogue by **tempol** in non-small-cell lung cancer cell lines under hypoxia.
AU Bando T; Kasahara K; Shibata K; Numata Y; Heki U; Shirasaki H; Iwasa K; Fujimura M; Matsuda T
CS Third Department of Internal Medicine, Kanazawa University School of Medicine, Japan.
SO JOURNAL OF CANCER RESEARCH AND CLINICAL ONCOLOGY, **(1996)**. Vol. 122, No. 1, pp. 21-6.
Journal code: HL5. ISSN: 0171-5216.
DT Journal; Article; (JOURNAL ARTICLE)
FS MEDL; L; Priority Journals; Cancer Journals
LA English
OS MEDLINE 96140768
EM 199603
AB We examined the mechanisms involved in the bioactivation of mitomycin C (MMC) and a newly developed MMC analogue: 7-N-(2-([2-(gamma-L-glutamylamino)ethyl]dithio)ethyl)mitomycin C, KW-2149, in non-small-cell lung cancer (NSCLC) cell lines under aerobic and hypoxic conditions. To investigate these mechanisms, we used MMC-resistant non-small-cell lung cancer cell lines (PC-9/MC4) that had been established in our laboratory from the parent PC-9 cell line by continuous exposure to MMC. We previously reported that the MMC-resistant cell line (PC-9/MC4) was poor in NAD(P)H dehydrogenase (quinone) activity and approximately 6-fold more resistant than the parent cells (PC-9) to MMC on 2-h exposure under aerobic conditions. In this study, the subline PC-9/MC4 was 6.7-fold more resistant to MMC than PC-9, the parent cell line, under aerobic conditions, and 5.2-fold more resistant under hypoxic conditions after 2-h exposure to MMC. However, on co-incubation with **tempol**, an inhibitor of the one-electron reduction pathway, the sensitivity of PC-9/MC4 to MMC was impaired under hypoxic conditions, but the impairment was not evident under aerobic conditions. KW-2149, the newly developed MMC analogue, was cytotoxic for both PC-9/MC4 and PC-9 cells, and the sensitivity of both cell lines to KW-2149 was not changed by exposure to hypoxic conditions or by coincubation with **tempol**. There were no significant differences in the intracellular uptake of MMC and the activities of cytosolic detoxification enzymes between the PC-9 and PC-9/MC4 cell lines. These results support the hypothesis that the one-electron reduction pathway plays a partial role in the bioactivation of MMC, but not of KW-2149, and that KW-2149 is excellent at circumventing resistance to MMC in NSCLC.
CT Check Tags: Human
*Antineoplastic Agents: PD, pharmacology
*Antioxidants: PD, pharmacology
Biotransformation
*Carcinoma, Non-Small-Cell Lung: DT, drug therapy
Carcinoma, Non-Small-Cell Lung: ME, metabolism
Carcinoma, Non-Small-Cell Lung: PA, pathology
Cell Division: DE, drug effects
Cell Hypoxia
*Cyclic N-Oxides: PD, pharmacology
Cytochrome Reductases: ME, metabolism
Drug Combinations
Drug Resistance, Neoplasm
*Lung Neoplasms: DT, drug therapy
Lung Neoplasms: ME, metabolism

Lung Neoplasms: PA, pathology
*Mitomycin: AA, analogs & derivatives
*Mitomycin: PD, pharmacology
NAD(P)H Dehydrogenase (Quinone): ME, metabolism
Tumor Cells, Cultured: DE, drug effects
RN 118359-59-4 (KW 2149); **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; 50-07-7 (Mitomycin)
CN EC 1.6.2. (Cytochrome Reductases); EC 1.6.2.2 (cytochrome b(5) reductase); EC 1.6.99.2 (NAD(P)H Dehydrogenase (Quinone)); 0 (Antineoplastic Agents); 0 (Antioxidants); 0 (Cyclic N-Oxides); 0 (Drug Combinations)

L125 ANSWER 5 OF 13 CANCERLIT
AN 95391709 CANCERLIT
DN 95391709
TI Pronounced activation of protein kinase C, ornithine decarboxylase and c-jun proto-oncogene by paraquat-generated active oxygen species in WI-38 human lung cells.
AU Kuo M L; Lee K C; Lin J K; Huang T S
CS Institute of Toxicology, college of Medicine National Taiwan University, Taipei, Republic of China.
SO BIOCHIMICA ET BIOPHYSICA ACTA, **(1995)**. Vol. 1268, No. 2, pp. 229-36.
Journal code: A0W. ISSN: 0006-3002.
DT Journal; Article; (JOURNAL ARTICLE)
FS MEDL; L; Priority Journals; Cancer Journals
LA English
OS MEDLINE 95391709
EM 199511
AB Paraquat (methyl viologen, PQ) is a widely used herbicide that produces oxygen-derived free radicals and severely injures human lungs. In this study we examined the effects of PQ on the protein kinase C (PKC), ornithine decarboxylase (ODC) and c-jun oncogene expression in WI-38 human lung cells. Exposure of cells to 25-200 microM PQ resulted in an increase of [3H]phorbol dibutyrate (PDBu) binding and PKC redistribution in a dose-dependent manner. Interestingly, a superoxide dismutase mimic, 4-hydroxyl-2,2,6,6-tetramethyl-piperidine-1-oxyl (**Tempol**, 2.5 mM) and catalase (400 micrograms/ml) could significantly reduce the PQ-stimulated increase of phorbol ester binding and particular PKC phosphorylating activity, but dimethylsulfoxide (DMSO, 1.5%), an effective .OH trapping agent, failed to prevent this stimulation. In addition, an endogenous substrate of PKC, 80 kDa protein, was found to be highly phosphorylated in intact WI-38 cells treated with 50 microM PQ. The increase of phosphorylated proteins could be completely or partly abolished by **Tempol** or catalase, but only the phosphorylation of 80 kDa protein was diminished by protein kinase C inhibitor, 1-(5-isoquinolinyl-sulfonyl)-2-methylpiperazine (H-7). A maximal peak of ODC activity was observed at 6 h of treatment with 50 microM PQ. PQ induced activity was reduced at the following rates, **Tempol** 85%, DMSO 80% and catalase 45%, but H-7 failed to do so. Furthermore, we found that the level of c-jun mRNA was transiently increased by PQ and the peak appeared at 1 h of treatment. When correlated with the PKC result, **Tempol**, catalase and H-7 all effectively blocked PQ-elicited c-jun transcript expression, but DMSO only exhibited a weakly inhibitory effect. We therefore propose that superoxide anion (O2- and H2O2 generated by PQ could activate PKC and lead to induction of c-jun gene expression; on the other hand, O2- and .OH might trigger other kinase pathways to elevate ODC activity. Finally, the sequential expression of c-jun oncogene and ODC may cooperate to relieve the oxidative damages elicited by PQ.
CT Check Tags: Human; Support, Non-U.S. Gov't
Cell Line
Enzyme Activation
Gene Expression: DE, drug effects
***Genes, jun**
Kinetics
*Lung: DE, drug effects
Lung: ME, metabolism

*Ornithine Decarboxylase: ME, metabolism
*Paraquat: TO, toxicity
*Protein Kinase C: ME, metabolism
*Reactive Oxygen Species: ME, metabolism
RN 4685-14-7 (Paraquat)
CN EC 2.7.1.- (Protein Kinase C); EC 4.1.1.17 (Ornithine Decarboxylase); 0 (Reactive Oxygen Species)

L125 ANSWER 6 OF 13 CANCERLIT
AN 95228014 CANCERLIT
DN 95228014
TI Protection from radiation-induced chromosomal aberrations by the nitroxide **Tempol**.
AU Johnstone P A; DeGraff W G; Mitchell J B
CS Radiation Biology Branch, National Cancer Institute, Bethesda, Maryland 20892, USA.
SO CANCER, **(1995)**. Vol. 75, No. 9, pp. 2323-7.
Journal code: CLZ. ISSN: 0008-543X.
DT Journal; Article; (JOURNAL ARTICLE)
FS MEDL; L; Abridged Index Medicus Journals; Priority Journals; Cancer Journals
LA English
OS MEDLINE 95228014
EM 199506
AB BACKGROUND. The nitroxide **Tempol** (4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl) is a stable, free radical that exhibits protection from ionizing radiation damage and from oxidative stress mediated through exposure of cells to superoxide or hydrogen peroxide. Radiation protection has been observed in both in vivo and in vitro models. To understand the mechanism of **Tempol**-mediated radioprotection better, the production of radiation-induced chromosome aberrations was evaluated. This study analyzed **Tempol**-mediated radioprotection of human peripheral blood lymphocytes (PBLs). METHODS. Peripheral blood lymphocytes were exposed to control (0mM), 10 mM (Tp10), and 50 mM (Tp50) concentrations of **Tempol** for 20 minutes before irradiation with 0, 150, 300, and 450 cGy. One quarter ml whole blood was cultured in F12 medium and phytohemagglutinin at 37 degrees C for 49, 54, 59, and 64 hours. Colcemide was added to each sample for the last 5 hours before harvest. Cells were harvested, treated with hypotonic solution, and fixed before dropping on cold clean slides. Mitotic indices and frequency of dicentric, ring, and triradial chromosomal aberrations were determined at 1000x magnification for each treatment group at each collection point. RESULTS. Treatment of cells with **Tempol** alone did not induce the chromosomal aberration frequency above that for unirradiated controls. Radiation dose response curves for total chromosome aberration production revealed radioprotection for **Tempol** treatment for both 10 and 50 mM exposures. **Tempol** protection factors (assessed at 0.2 aberrations/cell level) for Tp 10 and Tp 50 were 2.2 and 2.8, respectively. CONCLUSIONS. **Tempol** protects against radiation-induced chromosome aberrations in human PBLs. This finding is consistent with and lends support to previous studies in which **Tempol** was reported to enhance cell survival and reduce radiation-induced DNA double strand breaks.
CT Check Tags: Human; Male
Cell Survival: DE, drug effects
Cell Survival: RE, radiation effects
***Chromosome Aberrations**
*Chromosomes: DE, drug effects
*Chromosomes: RE, radiation effects
Cyclic N-Oxides: AD, administration & dosage
*Cyclic N-Oxides: PD, pharmacology
Dose-Response Relationship, Drug
Dose-Response Relationship, Radiation
DNA: DE, drug effects
DNA: RE, radiation effects
DNA Damage

Free Radicals: AD, administration & dosage
Free Radicals: PD, pharmacology
*Lymphocytes: DE, drug effects
*Lymphocytes: RE, radiation effects
Metaphase
Mitotic Index
Radiation Dosage
Radiation-Protective Agents: AD, administration & dosage
*Radiation-Protective Agents: PD, pharmacology
Regression Analysis
RN **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; 9007-49-2 (DNA)
CN 0 (Cyclic N-Oxides); 0 (Free Radicals); 0 (Radiation-Protective Agents)

L125 ANSWER 7 OF 13 CANCERLIT
AN 95032187 CANCERLIT
DN 95032187
TI Free radical modes of cytotoxicity of adriamycin and streptonigrin.
AU DeGraff W; Hahn S M; Mitchell J B; Krishna M C
CS Radiation Biology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892.
SO BIOCHEMICAL PHARMACOLOGY, **(1994)**. Vol. 48, No. 7, pp. 1427-35. Journal code: 9Z4. ISSN: 0006-2952.
DT Journal; Article; (JOURNAL ARTICLE)
FS MEDL; L; Priority Journals; Cancer Journals
LA English
OS MEDLINE 95032187
EM 199412
AB Free radical modes of cytotoxicity of streptonigrin (STN) and Adriamycin (ADR) in Chinese hamster V79 cells under aerobic conditions were evaluated using 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (TP), a low molecular weight stable nitroxide free radical with antioxidant properties and desferrioxamine (DF), a **transition metal** chelator. In addition, exogenous superoxide dismutase (SOD, EC 1.15.1.1) and catalase (CAT, EC 1.11.1.6), were tested for cytoprotective effects. EPR studies showed that TP reacts with the semiquinones of both ADR and STN and also with O2- radicals generated during aerobic redox cycling of the respective semiquinone radicals. Pulsed field gel electrophoresis studies confirmed that DNA double-strand breaks (dsb) induced by STN in V79 cells were inhibited completely by TP, whereas ADR-induced DNA dsb were not affected by TP. Clonogenic cell survival studies showed that STN-induced cytotoxicity could be inhibited completely by DF or TP. Both agents were ineffective in inhibiting ADR-induced cytotoxicity. SOD and CAT were ineffective in protecting against both STN and ADR cytotoxicity. Our results are consistent with a mechanism requiring the semiquinone radical intermediate of STN for cytotoxicity and minimal free radical involvement in ADR-induced V79 cell cytotoxicity.
CT Check Tags: Animal
Catalase: PD, pharmacology
Cell Line
Cell Survival: DE, drug effects
Cricetulus
Cyclic N-Oxides: AI, antagonists & inhibitors
Cyclic N-Oxides: PD, pharmacology
Deferoxamine: PD, pharmacology
Dose-Response Relationship, Drug
*Doxorubicin: PD, pharmacology
DNA Damage
Electron Spin Resonance Spectroscopy
Free Radicals
Hamsters
NADH Dehydrogenase
Quinones: CH, chemistry
Spin Labels
Streptonigrin: AI, antagonists & inhibitors
*Streptonigrin: PD, pharmacology

Superoxide Dismutase: PD, pharmacology
RN **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; 23214-92-8 (Doxorubicin); 3930-19-6 (Streptonigrin); 70-51-9 (Deferoxamine)
CN EC 1.11.1.6 (Catalase); EC 1.15.1.1 (Superoxide Dismutase); EC 1.6.99.3 (NADH Dehydrogenase); 0 (Cyclic N-Oxides); 0 (Free Radicals); 0 (Quinones); 0 (Spin Labels)

L125 ANSWER 8 OF 13 CANCERLIT
AN 94338702 CANCERLIT
DN 94338702
TI Selective potentiation of NMDA-induced neuronal injury following induction of astrocytic iNOS.
AU Hewett S J; Csernansky C A; Choi D W
CS Department of Neurology, Washington University School of Medicine, St. Louis, Missouri 63110.
NC DA 07261 (NIDA)
NS 07027 (NINDS)
NS 30337 (NINDS)
SO NEURON, **(1994)**. Vol. 13, No. 2, pp. 487-94.
Journal code: AN8. ISSN: 0896-6273.
DT Journal; Article; (JOURNAL ARTICLE)
FS MEDL; L; Priority Journals
LA English
OS MEDLINE 94338702
EM 199410
AB Nitric oxide (NO) produced by the constitutive NO synthase (cNOS) in neurons has been implicated in mediating excitotoxic neuronal death. In our murine cortical cell culture system, NMDA neurotoxicity was not blocked by addition of the NOS inhibitors, NG-nitro-L-arginine or aminoguanidine. However, following activation of inducible NOS in astrocytes by interleukin-1 beta plus interferon-gamma, NMDA but not kainate neurotoxicity was markedly potentiated. This selective potentiation of NMDA neurotoxicity was blocked by NOS inhibition or antioxidants (superoxide dismutase/catalase or **Tempol**) and could be mimicked by NO generators (SIN-1 or SNAP) or the oxygen radical generator, pyragallol. These results raise the possibility that NO production by astrocytes may contribute to NMDA receptor-mediated neuronal death, perhaps through interaction with oxygen radicals.
CT Check Tags: Animal; In Vitro; Support, U.S. Gov't, P.H.S.
*Amino Acid Oxidoreductases: PH, physiology
*Astrocytes: EN, enzymology
Cell Death: DE, drug effects
Cells, Cultured
Drug Synergism
Enzyme Induction
Interferon Type II: PD, pharmacology
Interleukin-1: PD, pharmacology
Kainic Acid: TO, toxicity
Mice
Molsidomine: AA, analogs & derivatives
Molsidomine: PD, pharmacology
N-Methylaspartate: TO, toxicity
*Neurons: DE, drug effects
Nitric Oxide: PH, physiology
Penicillamine: AA, analogs & derivatives
Penicillamine: PD, pharmacology
RN 10102-43-9 (Nitric Oxide); 25717-80-0 (Molsidomine); 33876-97-0 (CV 664); 487-79-6 (Kainic Acid); 52-67-5 (Penicillamine); 6384-92-5 (N-Methylaspartate); 79032-48-7 (S-nitroso-N-acetylpenicillamine); 82115-62-6 (Interferon Type II)
CN EC 1.14.13.39 (Nitric-Oxide Synthase); EC 1.4. (Amino Acid Oxidoreductases); 0 (Interleukin-1)

L125 ANSWER 9 OF 13 CANCERLIT
AN 94311588 CANCERLIT
DN 94311588

TI Effects of nitroxide stable radicals on juglone cytotoxicity.
AU Zhang R; Hirsch O; Mohsen M; Samuni A
CS Molecular Biology, School of Medicine, Hebrew University, Jerusalem, Israel.
SO ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS, **(1994)**. Vol. 312, No. 2, pp. 385-91.
Journal code: 6SK. ISSN: 0003-9861.
DT Journal; Article; (JOURNAL ARTICLE)
FS MEDL; L; Priority Journals; Cancer Journals
LA English
OS MEDLINE 94311588
EM 199409
AB Nitroxides stable radicals are unreactive toward most diamagnetic molecules, but readily undergo one-electron redox reactions with paramagnetic species such as free radicals and **transition metals**, thus serving as cell-permeable antioxidants. The cytotoxicity of juglone (5-hydroxy-1,4-naphthoquinone), like that of other naphthoquinones, requires bioreduction to yield the semiquinone which in turn reduces oxygen to O2.-. Therefore, nitroxides are expected to mitigate cytotoxicity of quinone-based xenobiotics, such as naphthoquinones. In the present study, in vitro scission of isolated DNA was induced upon juglone reduction by glutathione and Fe(II) ions, however, not by xanthine oxidase or cytochrome c reductase. The DNA scission was inhibited by nitroxides, catalase and chelating agents, though not by superoxide dismutase. Juglone was more toxic toward bacterial cells under hypoxia than under air. Nitroxides < or = 2 mM protected bacterial cells from juglone-induced toxicity under both aerobic and hypoxic conditions. The cytoprotective effect of lipophilic nitroxide was greater than that of hydrophilic ones. Catalase and metal chelating agents decreased juglone-induced cell killing, whereas H2O2 increased it. The mechanisms underlying the nitroxides protective effect involve (a) the reoxidation of reduced **transition metal** ions, (b) the selective radical-radical reaction with juglone semiquinone, and possibly (c) under aerobic condition catalytic removal of extra- and intracellular O2.-. The present results suggest also that the cell membrane rather than DNA is the main target of juglone toxicity.
CT Check Tags: Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.
Catalase: ME, metabolism
Cyclic N-Oxides: PD, pharmacology
Drug Interactions
DNA Damage: DE, drug effects
Escherichia coli: DE, drug effects
Free Radicals
Hydrogen Peroxide: ME, metabolism
Naphthoquinones: CH, chemistry
*Naphthoquinones: TO, toxicity
Nitrogen Oxides: CH, chemistry
*Nitrogen Oxides: PD, pharmacology
Spin Labels
Spiro Compounds: PD, pharmacology
Superoxide Dismutase: ME, metabolism
RN 133906-30-6 (2-spirocyclohexane doxyl (2-spirocyclohexane-5,5-dimethyl-3-oxazolidinoxyl)); 14691-88-4 (tempamine); **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; 481-39-0 (juglone); 7722-84-1 (Hydrogen Peroxide)
CN EC 1.11.1.6 (Catalase); EC 1.15.1.1 (Superoxide Dismutase); 0 (Cyclic N-Oxides); 0 (Free Radicals); 0 (Naphthoquinones); 0 (Nitrogen Oxides); 0 (Spin Labels); 0 (Spiro Compounds)

L125 ANSWER 10 OF 13 CANCERLIT
AN 94192631 CANCERLIT
DN 94192631
TI Polymerase chain reaction-directed DNA sequencing of bleomycin-induced "nondeletion"-type, 6-thioguanine-resistant mutants in Chinese hamster ovary cell derivative AS52: effects of an inhibitor and a mimic of superoxide dismutase.

AU An J; Hsie A W
CS Department of Preventive Medicine and Community Health, University of Texas Medical Branch, Galveston 77555-1010.
NC 1RO1CA56434-01 (NCI)
SO ENVIRONMENTAL AND MOLECULAR MUTAGENESIS, **(1994)**. Vol. 23, No. 2, pp. 101-9.
Journal code: EMM. ISSN: 0893-6692.
DT Journal; Article; (JOURNAL ARTICLE)
FS MEDL; L; Priority Journals; Cancer Journals
LA English
OS MEDLINE 94192631
EM 199406
AB Bleomycin-induced, 6-thioguanine-resistant, "non deletion" mutants pretreated with or without either TRIEN (triethylenetetramine), a superoxide dismutase (SOD) inhibitor, or **TEMPOL** (4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl), a SOD mimic, were analyzed by polymerase chain reaction (PCR)-directed DNA sequencing in a Chinese hamster ovary (CHO) cell derivative, AS52. Among the 23 bleomycin-induced mutants, six have 3-bp 5'-TGA-3' deletions in the region of 366-371, five have single-base deletions, seven have base substitutions, three have insertions, and two have possible translocations. Among the 16 bleomycin-induced mutants pretreated with TRIEN, six have the 5'-TGA-3' deletion (366-371), two have single-base deletions, one has a 13-bp deletion, four have single-base substitutions, one has a double-base substitution, and two have insertions. Among the 17 bleomycin-induced mutants pretreated with **TEMPOL**, six have the same TGA deletions, two have single-base deletions, two have single-base insertions, four have single-base substitutions, one mutant has a 12-bp deletion, one has a 13-bp deletion, and one mutant shows no detectable change in its coding region in the DNA sequence. A possible shift from a ROS-mediated mutational spectrum to a spontaneous mutational spectrum by TRIEN further indicates that reactive oxygen species play an important role in bleomycin mutagenesis in mammalian cells.
CT Check Tags: Animal; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.
Base Sequence
*Bleomycin: TO, toxicity
*Cyclic N-Oxides: PD, pharmacology
CHO Cells
DNA
*DNA Mutational Analysis
Frameshift Mutation
Hamsters
Molecular Sequence Data
Oxidation-Reduction
Pentosyltransferases: GE, genetics
Polymerase Chain Reaction
Sequence Analysis, DNA
Sequence Deletion
Superoxide Dismutase: AI, antagonists & inhibitors
Superoxide Dismutase: DE, drug effects
*Superoxide Dismutase: ME, metabolism
Thioguanine: PD, pharmacology
*Triethylenetetramine: PD, pharmacology
RN 11056-06-7 (Bleomycin); 112-24-3 (Triethylenetetramine); 154-42-7 (Thioguanine); **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; 9007-49-2 (DNA)
CN EC 1.15.1.1 (Superoxide Dismutase); EC 2.4.2. (Pentosyltransferases); EC 2.4.2.22 (xanthine phosphoribosyltransferase); 0 (Cyclic N-Oxides)
GEN gpt

L125 ANSWER 11 OF 13 CANCERLIT
AN 93390545 CANCERLIT
DN 93390545
TI Polymerase chain reaction-based deletion screening of bleomycin induced 6-thioguanine-resistant mutants in Chinese hamster ovary cells: the

effects of an inhibitor and a mimic of superoxide dismutase.
AU An J; Hsie A W
CS Department of Preventive Medicine and Community Health, University of Texas Medical Branch, Galveston 77555-1010.
SO MUTATION RESEARCH, **(1993)**. Vol. 289, No. 2, pp. 215-22.
Journal code: NNA. ISSN: 0027-5107.
DT Journal; Article; (JOURNAL ARTICLE)
FS MEDL; L; Priority Journals; Cancer Journals
LA English
OS MEDLINE 93390545
EM 199311
AB Bleomycin-induced 6-thioguanine-resistant mutants pretreated with or without TRIEN (triethylenetetramine), a superoxide dismutase (SOD) inhibitor, or **TEMPOL** (4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl), an SOD mimic, were analyzed by polymerase chain reaction (PCR)-based deletion screening in a Chinese hamster ovary (CHO) clone K1-BH4 and its derivative AS52 cells. As we proposed earlier, TRIEN would decrease and **TEMPOL** would increase the intracellular level of hydroxyl radical leading to a higher and lower recovery of deletion mutants. We found that the proportion of the deletion mutants induced by bleomycin at the hypoxanthine-guanine phosphoribosyltransferase (hprt) locus in K1-BH4 cells was 45.5% (25/55). The proportion of deletion HPRT- mutants induced by bleomycin pretreated with TRIEN was 31.0% (9/29) and with **TEMPOL** was 50.0% (14/28). The proportion of deletion mutants induced by bleomycin on the xanthine-guanine phosphoribosyltransferase (gpt) gene in AS52 cells was 61.0% (36/59). The proportion of deletion GPT- mutants induced by bleomycin pretreated with TRIEN was 56.8% (21/37) and with **TEMPOL** was 61.4% (27/44). The trend of the change of the proportion of bleomycin-induced deletion mutants as affected by TRIEN and by **TEMPOL** provides molecular evidence for the involvement of reactive oxygen species (ROS) in bleomycin mutagenesis in mammalian cells, in which deletion is a major type of induced mutation.
CT Check Tags: Animal; Support, Non-U.S. Gov't
Base Sequence
*Bleomycin: TO, toxicity
Cricetulus
Cyclic N-Oxides: PD, pharmacology
CHO Cells
DNA Mutational Analysis
Hamsters
Hypoxanthine Phosphoribosyltransferase: GE, genetics
Molecular Sequence Data
***Mutagenesis**
Pentosyltransferases: GE, genetics
Polymerase Chain Reaction
*Reactive Oxygen Species: ME, metabolism
***Sequence Deletion**
Superoxide Dismutase: AI, antagonists & inhibitors
*Superoxide Dismutase: ME, metabolism
Thioguanine: PD, pharmacology
Triethylenetetramine: PD, pharmacology
RN 11056-06-7 (Bleomycin); 112-24-3 (Triethylenetetramine); 154-42-7 (Thioguanine); **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**
CN EC 1.15.1.1 (Superoxide Dismutase); EC 2.4.2. (Pentosyltransferases); EC 2.4.2.22 (xanthine phosphoribosyltransferase); EC 2.4.2.8 (Hypoxanthine Phosphoribosyltransferase); 0 (Cyclic N-Oxides); 0 (Reactive Oxygen Species)

L125 ANSWER 12 OF 13 CANCERLIT
AN 93249974 CANCERLIT
DN 93249974
TI **Tempol** and deferoxamine protect cultured rabbit lens epithelial cells from H2O2 insult: insight into the mechanism of H2O2-induced injury.
AU Reddan J; Sevilla M; Giblin F; Padgaonkar V; Dziedzic D; Leverenz V

CS Department of Biological Sciences, Oakland University, Rochester, Michigan 48309-4401.
NC EY00362 (NEI)
EY02027 (NEI)
EY05230 (NEI)
SO LENS AND EYE TOXICITY RESEARCH, **(1992)**. Vol. 9, No. 3-4, pp. 385-93.
Journal code: AZF. ISSN: 1042-6922.
DT Journal; Article; (JOURNAL ARTICLE)
FS MEDL; L; Priority Journals
LA English
OS MEDLINE 93249974
EM 199307
AB In order to investigate the mechanism by which H2O2 damages the epithelium, 8 x 10(5) rabbit lens epithelial cells were treated with **TEMPOL** or deferoxamine and exposed to a single sublethal dose of 0.5 mM H2O2. **TEMPOL** is a SOD mimic, has a characteristic EPR spectrum and is metal independent. EPR spectra indicated that **TEMPOL** was not destroyed by H2O2, catalyzed the destruction of the superoxide anion, and penetrated the cells. Cells treated with H2O2 showed membrane blebbing, growth inhibition, an increase in GSSG, a dose-dependent decrease in GSH, ATP, NAD+, and in the activity of G3PDH, and in lactate production. H2O2 stimulated the hexose mono-phosphate shunt and induced single strand breaks in DNA. Treatment with **TEMPOL** or deferoxamine prevented or curtailed H2O2-induced inhibition of growth, the decrease in NAD+, the induction of single strand breaks in DNA, and membrane blebbing, but not the other biochemical parameters investigated. Both **TEMPOL** and deferoxamine prevent Fe+2-mediated generation of the damaging hydroxyl radical. **TEMPOL** reacts with superoxide and thus prevents it from recycling Fe+3 to Fe+2. It also oxidizes DNA-Fe+2 to DNA-Fe+3. Deferoxamine chelates intracellular Fe+3 and prevents its reduction to Fe+2. These compounds which limit the availability of Fe+2 by different means indicate that **transition metals** (including those bound to DNA) mediate certain of the damaging effects of H2O2.
CT Check Tags: Animal; Comparative Study; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Adenosine Triphosphate: ME, metabolism
Cell Division: DE, drug effects
Cell Line
Cells, Cultured
*Cyclic N-Oxides: PD, pharmacology
*Deferoxamine: PD, pharmacology
DNA Damage: DE, drug effects
Epithelium: DE, drug effects
Epithelium: ME, metabolism
Glutathione: ME, metabolism
Glyceraldehyde-3-Phosphate Dehydrogenases: ME, metabolism
*Hydrogen Peroxide: AI, antagonists & inhibitors
Hydrogen Peroxide: TO, toxicity
*Lens, Crystalline: DE, drug effects
Lens, Crystalline: ME, metabolism
Mitosis: DE, drug effects
Rabbits
Superoxides: ME, metabolism
RN 11062-77-4 (Superoxides); **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; 56-65-5 (Adenosine Triphosphate); 70-18-8 (Glutathione); 70-51-9 (Deferoxamine); 7722-84-1 (Hydrogen Peroxide)
CN EC 1.2.1.- (Glyceraldehyde-3-Phosphate Dehydrogenases); 0 (Cyclic N-Oxides)

L125 ANSWER 13 OF 13 CANCERLIT
AN 93093491 CANCERLIT
DN 93093491
TI Nitroxide-mediated protection against X-ray- and neocarzinostatin-induced DNA damage.

AU DeGraff W G; Krishna M C; Kaufman D; Mitchell J B
CS Radiobiology Section, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892.
SO FREE RADICAL BIOLOGY AND MEDICINE, **(1992)**. Vol. 13, No. 5, pp. 479-87.
Journal code: FRE. ISSN: 0891-5849.
DT Journal; Article; (JOURNAL ARTICLE)
FS MEDL; L; Priority Journals
LA English
OS MEDLINE 93093491
EM 199302
AB The stable free radical **Tempol** (4-hydroxy-2,2,6,6-tetramethyl-piperidinyloxy) has been shown to protect against X-ray-induced cytotoxicity and hydrogen peroxide- or xanthine oxidase-induced cytotoxicity and mutagenicity. The ability of **Tempol** to protect against X-ray- or neocarzinostatin (NCS)-induced mutagenicity or DNA double-strand breaks (dsb) was studied in Chinese hamster cells. **Tempol** (50 mM) provided a protection factor of 2.7 against X-ray-induced mutagenicity in Chinese hamster ovary (CHO) AS52 cells, with a protection factor against cytotoxicity of 3.5. Using the field inversion gel electrophoresis technique of measuring DNA dsb, 50 mM **Tempol** provides a threefold reduction in DNA damage at an X-ray dose of 40 Gy. For NCS-induced damage, **Tempol** increased survival from 9% to 80% at 60 ng/mL NCS and reduced mutation induction by a factor of approximately 3. DNA dsb were reduced by a factor of approximately 7 at 500 ng/mL NCS. **Tempol** is representative of a class of stable nitroxide free radical compounds that have superoxide dismutase-mimetic activity, can oxidize metal ions such as ferrous iron that are complexed to DNA, and may also detoxify radiation-induced organoperoxide radicals by competitive scvenging. The NCS chromophore is reduced by sulfhydryls to an active form. Electron spin resonance (ESR) spectroscopy shows that 2-mercaptoethanol-activated NCS reacts with **Tempol** 3.5 times faster than does unactivated NCS. Thus, **Tempol** appears to inactivate the NCS chromophore before a substantial amount of DNA damage occurs.
CT Check Tags: Animal
Cell Line
Cell Survival: DE, drug effects
*Cell Survival: RE, radiation effects
*Cyclic N-Oxides: PD, pharmacology
CHO Cells
Dose-Response Relationship, Drug
Dose-Response Relationship, Radiation
*DNA: DE, drug effects
*DNA: RE, radiation effects
***DNA Damage**
Hamsters
Kinetics
Mutagenesis
*Radiation-Protective Agents: PD, pharmacology
X-Rays
*Zinostatin: PD, pharmacology
RN **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; 9007-49-2 (DNA); 9014-02-2 (Zinostatin)
CN 0 (Cyclic N-Oxides); 0 (Radiation-Protective Agents)

=> fil medline

FILE 'MEDLINE' ENTERED AT 13:45:54 ON 30 JAN 2001

FILE LAST UPDATED: 27 OCT 2000 (20001027/UP). FILE COVERS 1960 TO DATE.

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The OLDMEDLINE file segment now contains data from 1958 through 1965.
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=> d all tot l127

L127 ANSWER 1 OF 11 MEDLINE
AN 1998062483 MEDLINE
DN 98062483
TI Detection and analyses of ascorbyl radical in cerebrospinal fluid and serum of acute lymphoblastic leukemia.
AU Nakagawa K; Kanno H; Miura Y
CS Radio Isotope Research Center, Department of Pediatrics, Fukushima Medical College, 1 Hikarigaoka, Fukushima-shi, 960-12, Japan.. nakagawa@cc.fmu.ac.jp
SO ANALYTICAL BIOCHEMISTRY, **(1997 Dec 1)** 254 (1) 31-5.
Journal code: 4NK. ISSN: 0003-2697.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199803
EW 19980305
AB We have detected and analyzed a free radical in human cerebrospinal fluid (CSF) of acute lymphoblastic leukemia (ALL) for the first time using electron paramagnetic resonance (EPR) at ambient temperature. We have also introduced an alternative capillary method to measure the radical. EPR spectra of the radical show a characteristic doublet with hyperfine coupling value of 1.8 G and g = 2.005. Based on EPR measurements, computer simulation, and literature values, we have determined that the species is ascorbyl radical (AsR). The radical has been investigated in CSF samples from ALL patients having no therapy, undergoing chemotherapy, and following therapy. Determination of the ascorbyl radical concentrations in CSF and serum was attempted using known concentrations of a nitroxyl radical. In addition, comparison in CSF and serum for ALL has been made along with statistical analyses of the data obtained. We found that AsR in CSF and serum has a strong correlation in patients undergoing chemotherapy ($n = 57$, $r = 0.57$, $P < 0.0001$). Ascorbate in CSF and serum show good correlation in patients having therapy but not for patients after therapy.

CT Check Tags: Female; Human; Male; Support, Non-U.S. Gov't
Antineoplastic Agents: TU, therapeutic use
*Ascorbic Acid: AN, analysis
Ascorbic Acid: BL, blood
Ascorbic Acid: CF, cerebrospinal fluid
Colorimetry: MT, methods
Cyclic N-Oxides
Electron Spin Resonance Spectroscopy
Free Radicals: AN, analysis
Leukemia, Lymphocytic, Acute: BL, blood
Leukemia, Lymphocytic, Acute: CF, cerebrospinal fluid
Leukemia, Lymphocytic, Acute: DT, drug therapy
***Leukemia, Lymphocytic, Acute: ME, metabolism**
Regression Analysis
Spin Labels
RN **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; 50-81-7

(Ascorbic Acid)
CN 0 (Antineoplastic Agents); 0 (Cyclic N-Oxides); 0 (Free Radicals); 0 (Spin Labels)

L127 ANSWER 2 OF 11 MEDLINE
AN 1998025416 MEDLINE
DN 98025416
TI **Tempol** inhibits neutrophil and hydrogen peroxide-mediated DNA damage.
AU Hahn S M; Mitchell J B; Shacter E
CS Radiation Biology Branch, National Cancer Institute, Bethesda, MD 20892, USA.
SO FREE RADICAL BIOLOGY AND MEDICINE, **(1997)** 23 (6) 879-84.
Journal code: FRE. ISSN: 0891-5849.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199801
EW 19980104
AB Inflammatory conditions characterized by neutrophil activation are associated with a variety of chronic diseases. Reactive oxygen species are produced by activated neutrophils and produce DNA damage which may lead to tissue damage. Previous studies have shown that activated murine neutrophils induce DNA strand breaks in a target plasmacytoma cell, RIMPC 2394. We studied the effect of a water soluble nitroxide anti-oxidant, **Tempol**, on murine neutrophil induction of DNA strand breaks in this system. Murine neutrophils were isolated from the peritoneal cavity of BALB/cAn mice after an i.p. injection of pristane oil. Neutrophils were activated by the phorbol ester PMA and co-incubated with RIMPC 2394 cells. Control alkaline elution studies revealed progressive DNA strand breaks in RIMPC cells with time. The addition of **Tempol** to the incubation mixture prevented DNA damage in a dose dependent fashion. Five mM **Tempol** provided complete protection. **Tempol** protection against DNA strand breaks was similar for both stimulated neutrophils and exogenously added hydrogen peroxide. Measurement of hydrogen peroxide produced by stimulated neutrophils demonstrated that **Tempol** did not decrease hydrogen peroxide concentration. Oxidation of reduced metals, thereby interfering with the production of hydroxyl radical, is the most likely mechanism of nitroxide protection, although superoxide dismutase (SOD) like activity and scavenging of carbon-based free radicals may also account for a portion of the observed protection. The anti-oxidant activity of **Tempol** inhibited DNA damage by activated neutrophils. The nitroxides as a class of compounds may have a role in the investigation and modification of inflammatory conditions.
CT Check Tags: Animal
*Antioxidants: PD, pharmacology
Cells, Cultured
*Cyclic N-Oxides: PD, pharmacology
*DNA Damage: DE, drug effects
*Hydrogen Peroxide: TO, toxicity
Mice
Mice, Inbred BALB C
Neutrophil Activation: DE, drug effects
*Neutrophils: DE, drug effects
Neutrophils: ME, metabolism
Peritoneal Cavity: CY, cytology
Plasmacytoma
Reactive Oxygen Species: ME, metabolism
Respiratory Burst: DE, drug effects
Tumor Cells, Cultured
RN **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; 7722-84-1 (Hydrogen Peroxide)
CN 0 (Antioxidants); 0 (Cyclic N-Oxides); 0 (Reactive Oxygen Species)

L127 ANSWER 3 OF 11 MEDLINE

AN 97252526 MEDLINE
DN 97252526
TI Evaluation of **tempol** radioprotection in a murine tumor model.
AU Hahn S M; Sullivan F J; DeLuca A M; Krishna C M; Wersto N; Venzon D; Russo A; Mitchell J B
CS Radiation Biology Branch, National Cancer Institute, Bethesda, MD 20892, USA.
SO FREE RADICAL BIOLOGY AND MEDICINE, **(1997)** 22 (7) 1211-6.
Journal code: FRE. ISSN: 0891-5849.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199710
EW 19971001
AB **Tempol**, a stable nitroxide free radical compound, is an in vitro and in vivo radioprotector. Previous studies have shown that **Tempol** protects C3H mice against whole-body radiation-induced bone marrow failure. In this study, the radioprotection of tumor tissue was evaluated. RIF-1 tumor cells were implanted in female C3H mice 10 d prior to radiation. Groups of mice were injected intraperitoneally with **Tempol** (275 mg/kg) or PBS followed 10 min later by a single dose of radiation to the tumor bed. Tumor growth curves generated after 10 and 33.3 Gy doses of radiation showed no difference in growth between the **Tempol**- and PBS-treated animals. A full radiation dose-response experiment revealed a tumor control dose in 50% of the animals in 30 d (TCD(50/30)) value of 36.7 Gy for **Tempol**-treated mice and 41.8 Gy for saline-treated mice suggesting no protection of the RIF-1 tumor by **Tempol**. Tumor pharmacokinetics were done to determine why **Tempol** differentially protected bone marrow and not tumor cells. Differential reduction of **Tempol** in the RIF-1 tumor and bone marrow was evaluated with EPR spectroscopy 10, 20, and 30 min after injection. Bioreduction of **Tempol** to its corresponding hydroxylamine (which is not a radioprotector) occurred to a greater extent in RIF-1 tumor cells compared to bone marrow. We conclude that the differences in radioprotection may result from enhanced intratumor bioreduction of **Tempol** to its nonradioprotective hydroxylamine analogue. The nitroxides as a class of compounds may provide a means to exploit the redox differences between normal tissues and tumors.
CT Check Tags: Animal; Female
Bone Marrow: DE, drug effects
Bone Marrow: RE, radiation effects
Cell Division: DE, drug effects
Cyclic N-Oxides: ME, metabolism
*Cyclic N-Oxides: PD, pharmacology
Cyclic N-Oxides: PK, pharmacokinetics
Electron Spin Resonance Spectroscopy
Mice
Mice, Inbred C3H
Neoplasm Transplantation
Neoplasms, Experimental: ME, metabolism
***Neoplasms, Experimental: PA, pathology**
Neoplasms, Experimental: RT, radiotherapy
*Radiation Tolerance: DE, drug effects
*Radiation-Protective Agents: PD, pharmacology
Radiation-Protective Agents: PK, pharmacokinetics
RN **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**
CN 0 (Cyclic N-Oxides); 0 (Radiation-Protective Agents)

L127 ANSWER 4 OF 11 MEDLINE
AN 97149761 MEDLINE
DN 97149761
TI Modulatory effect of **tempol** on toxicity and antitumor activity of 6-mercaptopurine and on P450 cytochrome level.
AU Konovalova N P; Diatchkovskaya R F; Volkova L M; Varfolomeev V N
CS Institute of Chemical Physics, Russian Academy of Sciences, Chernogolovka,

Moscow Region, Russia.
SO NEOPLASMA, **(1996)** 43 (5) 341-6.
Journal code: NVO. ISSN: 0028-2685.
CY Czech Republic
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199704
EW 19970402
AB Low selectivity of contemporary antitumor drugs requires a search for its improvement. In this context, nitroxyl radicals are of interest as promising pharmacological agents. The introduction of nitroxyl radical into the structure of antitumor cytostatics was found to reduce considerably their general and specific toxicity. In this work, we demonstrate a detoxifying effect of **tempol** upon its combined injection with cytostatics at their absolute lethal dose in the intact mice as well as an improvement of sensitivity of tumor-bearing animals to 6-MP. **Tempol** is shown to normalize the level of oxidized form of P450 cytochrome in a liver, reduced as a result of the injection of 6-MP.
CT Check Tags: Animal; Female
*Antimetabolites, Antineoplastic: PD, pharmacology
*Cyclic N-Oxides: PD, pharmacology
*Cytochrome P-450: DE, drug effects
Cytochrome P-450: ME, metabolism
Drug Synergism
*Liver: DE, drug effects
Liver: EN, enzymology
***Mammary Neoplasms, Experimental: DT, drug therapy**
***Mammary Neoplasms, Experimental: EN, enzymology**
Mice
Mice, Inbred C57BL
*6-Mercaptopurine: PD, pharmacology
RN **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; 50-44-2 (6-Mercaptopurine); 9035-51-2 (Cytochrome P-450)
CN 0 (Antimetabolites, Antineoplastic); 0 (Cyclic N-Oxides)

L127 ANSWER 5 OF 11 MEDLINE
AN 96374533 MEDLINE
DN 96374533
TI [Nitroxyl radical **Tempol** as a modulator of toxic and antineoplastic effect of 6-mercaptopurine].
Nitroksil'nyi radikal **tempol** kak moduliator toksicheskogo i protivoopukholevogo deistviia 6-merkaptopurina.
AU Konovalova N P; D'iachkovskaia R F; Volkova L M; Varfolomeev V N
SO VOPROSY ONKOLOGII, **(1996)** 42 (3) 57-63.
Journal code: XJU. ISSN: 0507-3758.
CY RUSSIA: Russian Federation
DT Journal; Article; (JOURNAL ARTICLE)
LA Russian
FS Priority Journals; Cancer Journals
EM 199612
AB Both intact mice and those with transplantable adenocarcinoma 755 were used in the investigation. The nitroxyl radical **Tempol** was shown to cut down the toxicity of 6-mercaptopurine and potentiate its antitumor effect to a certain degree. The study results suggest on the basis of an investigation of cytochrome P450 and some other evidence that said effect of **Tempol** might be due, at least, in part to antioxidant activity.
CT Check Tags: Animal; Male
***Adenocarcinoma: DT, drug therapy**
*Antimetabolites, Antineoplastic: TO, toxicity
*Antimetabolites, Antineoplastic: TU, therapeutic use
*Antineoplastic Agents: AI, antagonists & inhibitors
Antineoplastic Agents: TO, toxicity
*Antioxidants: PD, pharmacology
*Cyclic N-Oxides: PD, pharmacology

Dose-Response Relationship, Drug
Drug Administration Schedule
Drug Synergism
English Abstract
Mice
Mice, Inbred C57BL
Survival Analysis
*6-Mercaptopurine: AI, antagonists & inhibitors
6-Mercaptopurine: TO, toxicity
*6-Mercaptopurine: TU, therapeutic use
RN **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; 50-44-2 (6-Mercaptopurine)
CN 0 (Antimetabolites, Antineoplastic); 0 (Antineoplastic Agents); 0 (Antioxidants); 0 (Cyclic N-Oxides)

L127 ANSWER 6 OF 11 MEDLINE
AN 96200316 MEDLINE
DN 96200316
TI Adjunctive treatment of murine neuroblastoma with 6-hydroxydopamine and **Tempol**.
AU Purpura P; Westman L; Will P; Eidelman A; Kagan V E; Osipov A N; Schor N F
CS Department of Pediatrics, University of Pittsburgh, Pennsylvania 15213, USA.
NC CA47161 (NCI)
SO CANCER RESEARCH, **(1996 May 15)** 56 (10) 2336-42.
Journal code: CNF. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199608
AB Currently available therapy for disseminated neuroblastoma affords only a 5-20% 5-year survival rate. We have attempted to design targeted chemotherapy for this disease by exploiting the dopamine uptake system on neuroblastoma cells. 6-Hydroxydopamine (6OHDA) is a neurotransmitter analogue, which generates cytolytic oxygen radicals in neuroblastoma cells that take it up. It is, however, predictably, systemically toxic, because of its spontaneous oxidation. Its toxicity is particularly severe in the sympathetic nervous system, because this tissue selectively concentrates dopamine and its analogues. Lowering the dose of 6OHDA below toxic levels prohibitively compromises its antitumor effect. To avoid both the systemic and sympathetic nervous system toxicity yet retain the antitumor efficacy of 6OHDA, we have used the antioxidant **Tempol** adjunctively with 6OHDA. Administration of **Tempol** (250 mg/kg, i.p.) 10 min prior to administration of toxic doses of 6OHDA (350 or 400 mg/kg, i.p.) resulted in a decrease in the mortality rate, sympathetic nervous system impairment, and activity impairment compared with those seen with 6OHDA alone. Tumor weights from mice administered saline or **Tempol** alone were 3.6 +/- 1.9 and 2.9 +/- 0.7 g, respectively. In contrast, mice administered **Tempol** followed by 6OHDA had an average tumor weight of 0.7 +/- 0.3 g. Tumor incidence was also reduced from 80-100% to 40%. Studies performed using electron spin resonance spectroscopy suggest that **Tempol** acts in this system by reacting directly with both the 6OHDA radical and, in the presence of iron, its oxidation product, the hydroxyl radical.
CT Check Tags: Animal; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
*Adrenergic Agents: TU, therapeutic use
*Antioxidants: TU, therapeutic use
Blepharoptosis: CI, chemically induced
Catalase: PD, pharmacology
*Cyclic N-Oxides: TU, therapeutic use
*Dopamine: ME, metabolism
Drug Screening Assays, Antitumor
Electron Spin Resonance Spectroscopy
*Free Radical Scavengers: TU, therapeutic use

Iron: ME, metabolism
Mice
Mice, Inbred A
Neoplasm Transplantation
***Neuroblastoma: DT, drug therapy**
Neuroblastoma: ME, metabolism
*Neuroprotective Agents: TU, therapeutic use
Oxidopamine: TO, toxicity
*Oxidopamine: TU, therapeutic use
Peroxidase: PD, pharmacology
*Reactive Oxygen Species: ME, metabolism
Single-Blind Method
Spin Labels
Sympathetic Nervous System: DE, drug effects
RN 1199-18-4 (Oxidopamine); **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; 51-61-6 (Dopamine); 7439-89-6 (Iron)
CN EC 1.11.1.6 (Catalase); EC 1.11.1.7 (Peroxidase); 0 (Adrenergic Agents); 0 (Antioxidants); 0 (Cyclic N-Oxides); 0 (Free Radical Scavengers); 0 (Neuroprotective Agents); 0 (Reactive Oxygen Species); 0 (Spin Labels)

L127 ANSWER 7 OF 11 MEDLINE
AN 96140768 MEDLINE
DN 96140768
TI Modulation of sensitivity to mitomycin C and a dithiol analogue by **tempol** in non-small-cell lung cancer cell lines under hypoxia.
AU Bando T; Kasahara K; Shibata K; Numata Y; Heki U; Shirasaki H; Iwasa K; Fujimura M; Matsuda T
CS Third Department of Internal Medicine, Kanazawa University School of Medicine, Japan.
SO JOURNAL OF CANCER RESEARCH AND CLINICAL ONCOLOGY, **(1996)** 122 (1) 21-6.
Journal code: HL5. ISSN: 0171-5216.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199604
AB We examined the mechanisms involved in the bioactivation of mitomycin C (MMC) and a newly developed MMC analogue: 7-N-(2-([2-(gamma-L-glutamylamino)ethyl]dithio)ethyl)mitomycin C, KW-2149, in non-small-cell lung cancer (NSCLC) cell lines under aerobic and hypoxic conditions. To investigate these mechanisms, we used MMC-resistant non-small-cell lung cancer cell lines (PC-9/MC4) that had been established in our laboratory from the parent PC-9 cell line by continuous exposure to MMC. We previously reported that the MMC-resistant cell line (PC-9/MC4) was poor in NAD(P)H dehydrogenase (quinone) activity and approximately 6-fold more resistant than the parent cells (PC-9) to MMC on 2-h exposure under aerobic conditions. In this study, the subline PC-9/MC4 was 6.7-fold more resistant to MMC than PC-9, the parent cell line, under aerobic conditions, and 5.2-fold more resistant under hypoxic conditions after 2-h exposure to MMC. However, on co-incubation with **tempol**, an inhibitor of the one-electron reduction pathway, the sensitivity of PC-9/MC4 to MMC was impaired under hypoxic conditions, but the impairment was not evident under aerobic conditions. KW-2149, the newly developed MMC analogue, was cytotoxic for both PC-9/MC4 and PC-9 cells, and the sensitivity of both cell lines to KW-2149 was not changed by exposure to hypoxic conditions or by coincubation with **tempol**. There were no significant differences in the intracellular uptake of MMC and the activities of cytosolic detoxification enzymes between the PC-9 and PC-9/MC4 cell lines. These results support the hypothesis that the one-electron reduction pathway plays a partial role in the bioactivation of MMC, but not of KW-2149, and that KW-2149 is excellent at circumventing resistance to MMC in NSCLC.
CT Check Tags: Human
*Antineoplastic Agents: PD, pharmacology
*Antioxidants: PD, pharmacology

Biotransformation
***Carcinoma, Non-Small-Cell Lung: DT, drug therapy**
Carcinoma, Non-Small-Cell Lung: ME, metabolism
Carcinoma, Non-Small-Cell Lung: PA, pathology
Cell Division: DE, drug effects
Cell Hypoxia
*Cyclic N-Oxides: PD, pharmacology
Cytochrome Reductases: ME, metabolism
Drug Combinations
Drug Resistance, Neoplasm
***Lung Neoplasms: DT, drug therapy**
Lung Neoplasms: ME, metabolism
Lung Neoplasms: PA, pathology
*Mitomycin: AA, analogs & derivatives
*Mitomycin: PD, pharmacology
NAD(P)H Dehydrogenase (Quinone): ME, metabolism
Tumor Cells, Cultured: DE, drug effects
RN 118359-59-4 (KW 2149); **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; 50-07-7 (Mitomycin)
CN EC 1.6.2. (Cytochrome Reductases); EC 1.6.2.2 (cytochrome b(5) reductase); EC 1.6.99.2 (NAD(P)H Dehydrogenase (Quinone)); 0 (Antineoplastic Agents); 0 (Antioxidants); 0 (Cyclic N-Oxides); 0 (Drug Combinations)

L127 ANSWER 8 OF 11 MEDLINE
AN 96062613 MEDLINE
DN 96062613
TI [Nitroxyl radicals--modifiers of the toxic action of cytostatics]. Nitroksil'nye radikaly--modifikatory toksicheskogo deistviia tsitostatikov.
AU Konovalova N P
SO VOPROSY ONKOLOGII, **(1995)** 41 (2) 49-50.
Journal code: XJU. ISSN: 0507-3758.
CY RUSSIA: Russian Federation
DT Journal; Article; (JOURNAL ARTICLE)
LA Russian
FS Priority Journals; Cancer Journals
EM 199602
CT Check Tags: Animal
Adenocarcinoma: DT, drug therapy
*Antineoplastic Agents, Combined: TO, toxicity
Antineoplastic Agents, Combined: TU, therapeutic use
Cyclic N-Oxides: TU, therapeutic use
Drug Screening Assays, Antitumor
Drug Synergism
Drug Therapy, Combination
Free Radicals: TU, therapeutic use
*Nitrogen Oxides: TU, therapeutic use
RN 14332-28-6 (nitroxyl); **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**
CN 0 (Antineoplastic Agents, Combined); 0 (Cyclic N-Oxides); 0 (Free Radicals); 0 (Nitrogen Oxides)

L127 ANSWER 9 OF 11 MEDLINE
AN 94335598 MEDLINE
DN 94335598
TI Measurement of the intracellular concentration of oxygen in a cell perfusion system.
AU Chen K; Ng C E; Zweier J L; Kuppusamy P; Glickson J D; Swartz H M
CS Department of Radiology and Radiological Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland.
NC GM 34250 (NIGMS)
CA 51935 (NCI)
51950
+
SO MAGNETIC RESONANCE IN MEDICINE, **(1994 Jun)** 31 (6) 668-72.
Journal code: MHR. ISSN: 0740-3194.

CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199411
AB [O2] was measured in the embedding material (alginate) in a typical apparatus for conducting studies of viable cells with NMR, using low frequency EPR. In suspension cultures respiration was independent of [O2] in the perfusing media down to about 1 microM while in alginate beads, the comparable value was 70 microM, indicating that the alginate was a very substantial barrier to the free diffusion of oxygen. With knowledge of [O2] in the various compartments, [O2] in the perfusing medium can be increased and the full power of NMR can be used to provide information on metabolism under various conditions. These results also provide evidence supporting the feasibility and usefulness of EPR techniques using nitroxides to measure [O2] in macroscopic samples such as NMR perfusion tubes. This technique is rapid, apparently nonperturbing, and enables one to differentiate between the concentrations of oxygen in different compartments.
CT Check Tags: Animal; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Alginates
Cell Count
Culture Media
Cyclic N-Oxides: DU, diagnostic use
Diffusion
*Electron Spin Resonance Spectroscopy: MT, methods
Extracellular Space: ME, metabolism
Fibrosarcoma: ME, metabolism
Fibrosarcoma: PA, pathology
Kinetics
Mice
*Nuclear Magnetic Resonance: MT, methods
Oxygen: AD, administration & dosage
*Oxygen: AN, analysis
*Oxygen Consumption
Spin Labels
Surface Properties
Tumor Cells, Cultured
RN **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; 7782-44-7 (Oxygen); 9005-32-7 (alginic acid)
CN 0 (Alginates); 0 (Culture Media); 0 (Cyclic N-Oxides); 0 (Spin Labels)

L127 ANSWER 10 OF 11 MEDLINE
AN 94252906 MEDLINE
DN 94252906
TI Modification of the aerobic cytotoxicity of etanidazole.
AU Palayoor S T; Bump E A; Malaker K; Langley R E; Saroff D M; Delfs J R; Hurwitz S J; Coleman C N
CS Joint Center for Radiation Therapy, Harvard Medical School, Boston, MA 02115.
NC CA 42391 (NCI)
SO INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY, BIOLOGY, PHYSICS, **(1994 May 15)** 29 (2) 289-93.
Journal code: G97. ISSN: 0360-3016.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199409
AB PURPOSE: To determine the feasibility of modifying the aerobic cytotoxicity of etanidazole without interfering with the tumoricidal action of radiation plus etanidazole. METHODS AND MATERIALS: The aerobic cytotoxicity of etanidazole was studied using two different models: (1) Induction of apoptosis in EL4 cells: apoptotic DNA fragmentation was analyzed by agarose gel electrophoresis following 24 h treatment with etanidazole alone or in combination with various modifiers. (2) Spinal

cord neuronal loss in organotypic roller tube cultures: Survival of acetylcholinesterase positive ventral horn neurons was analyzed morphometrically following 72 h treatment with etanidazole alone or in combination with vitamin E succinate. RESULTS: Etanidazole (10 mM) induced apoptosis in EL4 cells. This effect was suppressed by 24 h treatment with TPA, IBMX, the free radical scavenger **TEMPOL** or vitamin E succinate. Vitamin E succinate also protected spinal cord cultures from etanidazole-induced neuronal loss. CONCLUSION: These results suggest that it might be possible to modify the neurotoxicity of etanidazole with agents that would not be expected to interfere with the tumoricidal action of radiation plus etanidazole.

CT Check Tags: Animal; Support, U.S. Gov't, P.H.S.
Aerobiosis
Apoptosis
Calcium: ME, metabolism
Cell Survival: DE, drug effects
*Etanidazole: PD, pharmacology
Lymphoma, T-Cell: PA, pathology
Mice
Superoxides: ME, metabolism
Tumor Cells, Cultured
Vitamin E: AA, analogs & derivatives
Vitamin E: PD, pharmacology

RN 11062-77-4 (Superoxides); 1406-18-4 (Vitamin E); 17407-37-3 (vitamin E succinate); 22668-01-5 (Etanidazole); 7440-70-2 (Calcium)

L127 ANSWER 11 OF 11 MEDLINE
AN 85200052 MEDLINE
DN 85200052
TI Differences in the reduction kinetics of incorporated spin labels in undifferentiated and differentiated mouse neuroblastoma cells.
AU Chen K Y; McLaughlin M G
NC CA 24479-05 (NCI)
RR 7058-15 (NCRR)
SO BIOCHIMICA ET BIOPHYSICA ACTA, **(1985 May 30)** 845 (2) 189-95.
Journal code: A0W. ISSN: 0006-3002.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 198509
AB Significant differences in the rate of reduction of two spin labels, 5-doxylstearic acid and **TEMPOL**, in the undifferentiated and differentiated NB-15 mouse neuroblastoma cells were demonstrated by using electron paramagnetic resonance (EPR) spectroscopy. The half-time (T1/2) values for decay of the EPR signal of 5-doxylstearic acid in the undifferentiated and differentiated neuroblastoma cells were 70 min and 290 min, respectively. The T1/2 values of **TEMPOL** in the undifferentiated and differentiated cells were 18 min and 34 min, respectively. The cellular reductant was characterized as non-protein-bound sulfhydryl groups. A corresponding difference in the cellular non-protein-bound sulfhydryl content, 19.30 nmol/mg protein for the undifferentiated cells and 6.78 nmol/mg protein for the differentiated cells, was observed. Comparison of the reduction rates of **TEMPOL** , 5-doxylstearic acid and 16-doxylstearic acid in the undifferentiated NB-15 cells suggested that the permeation of non-protein-bound sulfhydryl compounds from the cytosol to membrane may be responsible for the reduction of the lipid-soluble stearic acid spin labels.

CT Check Tags: Animal; Comparative Study; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Cell Differentiation
Cell Line
Cell Membrane: ME, metabolism
*Cyclic N-Oxides: ME, metabolism
Electron Spin Resonance Spectroscopy
Half-Life

Kinetics
Mice
***Neuroblastoma: ME, metabolism**
Neuroblastoma: PA, pathology
Oxidation-Reduction
Spin Labels
Sulfhydryl Compounds: ME, metabolism
RN **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; 29545-48-0 (5-doxylstearic acid); 53034-38-1 (16-nitroxystearic acid)
CN 0 (Cyclic N-Oxides); 0 (Spin Labels); 0 (Sulfhydryl Compounds)

=> fil wpids

FILE 'WPIDS' ENTERED AT 13:52:53 ON 30 JAN 2001
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FILE LAST UPDATED: 26 JAN 2001 <20010126/UP>
>>>UPDATE WEEKS:
MOST RECENT DERWENT WEEK 200106 <200106/DW>
DERWENT WEEK FOR CHEMICAL CODING: 200106
DERWENT WEEK FOR POLYMER INDEXING: 200106
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=> d all abeq tech tot

L135 ANSWER 1 OF 3 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1999-034089 [03] WPIDS
DNC C1999-010233
TI Preventing photo-ageing and other types of sun damage - by topical application of a composition containing 4-**hydroxy**-2,2,6,6-**tetra methyl-piperidinyl-oxy** free radical which blocks UV.
DC B03 D21 E13
IN BERNSTEIN, E
PA (UYJE-N) UNIV JEFFERSON THOMAS
CYC 1
PI US 5840734 A 19981124 (199903)* 5p A61K031-445
ADT US 5840734 A US 1997-851739 19970506
PRAI US 1997-851739 19970506
IC ICM A61K031-445
AB US 5840734 A UPAB: 19990122
Protecting humans exposed to sunlight against photoageing, sunburn and skin **cancer** comprises topical application of a **tempol** (i.e. 4-**hydroxy**-2,2,6,6-**tetramethyl-piperidinyloxy** free radical) (I) derivative. Also claimed are: (i) protecting individuals with a heightened sensitivity to the skin from damage resulting from the sun comprising topical administration of (I) to protect the skin against photoageing, sunburn and skin **cancer**; and (ii) a composition comprising (I) and a second sunscreen and an additive.
USE - The method is useful for preventing photoageing and other types of sun damage by topical application. (I) blocks UVB and protects against UVA in vitro and also acts as a free-radical scavenger. The compositions are useful for protecting individuals with heightened sensitivities to the

sun such as those undergoing psoralen treatment for **cancer**, psoriasis and other skin conditions, individuals undergoing photodynamic therapy for skin **cancer**, psoriasis or other skin condition, individuals suffering from genetic repair defects such as xeroderma pigmentosa, albinism or other conditions resulting from decreased endogenous melanin pigment.
Dwg.0/0
FS CPI
FA AB; DCN
MC CPI: B07-D05; **B14-H01**; B14-N17C; B14-R05; B14-S08; D08-B09A; E07-D05

L135 ANSWER 2 OF 3 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1997-558671 [51] WPIDS
DNC C1997-178339
TI Prevention of photo-ageing, sunburn and skin **cancer** - by topical application of hydroxy-tetra methyl piperidinyloxy containing composition.
DC B03 D21 E13
IN BERNSTEIN, E
PA (BERN-I) BERNSTEIN E F; (UYJE-N) UNIV JEFFERSON THOMAS
CYC 68
PI WO 9741826 A1 19971113 (199751)* EN 15p A61K007-00
RW: AT BE CH DE DK EA ES FI FR GB GH GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG
W: AL AU BA BB BG BR CA CN CU CZ EE GE GH HU IL IS JP KP KR LC LK LR LT LV MG MK MN MX NO NZ PL RO SG SI SK TR TT UA US UZ VN YU
AU 9730605 A 19971126 (199813) A61K007-00
EP 906078 A1 19990407 (199918) EN A61K007-00
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
AU 720476 B 20000601 (200035) A61K007-00
JP 2000511516 W 20000905 (200047) 14p A61K007-42
ADT WO 9741826 A1 WO 1997-US7699 19970506; AU 9730605 A AU 1997-30605 19970506; EP 906078 A1 EP 1997-925477 19970506, WO 1997-US7699 19970506; AU 720476 B AU 1997-30605 19970506; JP 2000511516 W JP 1997-540161 19970506, WO 1997-US7699 19970506
FDT AU 9730605 A Based on WO 9741826; EP 906078 A1 Based on WO 9741826; AU 720476 B Previous Publ. AU 9730605, Based on WO 9741826; JP 2000511516 W Based on WO 9741826
PRAI US 1996-16769 19960507
REP US 5462946; US 5569663
IC ICM A61K007-00; A61K007-42
ICS A61K007-40; A61K007-44; A61K031-445; A61P017-16
AB WO 9741826 A UPAB: 19971222
Prevention of photo-ageing and other sun damage comprises topical application of a composition containing **Tempol** (RTM; 4-hydroxy-2,2,6,6-tetramethyl piperidinyloxy, free radical) to the skin.
USE - Method prevents photo-ageing and blocks ultraviolet B radiation thus preventing sunburn or skin **cancer**. Method is used to prevent photo-ageing and other sun damage and to protect individuals with heightened sensitivity to the sun from damage caused by the sun (claimed), such as those undergoing psoralen treatment for **cancer**, psoriasis and other conditions, individuals undergoing photodynamic therapy for skin **cancer**, psoriasis and other conditions, individuals suffering from genetic repair defects such as xeroderma pigmentosa, albinism or other conditions resulting from decreases endogenous melanin pigment.
Dwg.0/0
FS CPI
FA AB; DCN
MC CPI: B07-D05; B14-N17; B14-R05; D08-B09A; E07-D05

L135 ANSWER 3 OF 3 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1997-051852 [05] WPIDS
DNC C1997-017130
TI Use of nitroxide cpds. against free radical-induced oxidative stress - due to ionising radiation, carcinogens, mutagens, ageing, arthritis and

reperfusion.
DC B03 B05
IN DEGRAFF, W G; HAHN, S; MITCHELL, J B; SAMUNI, A
PA (USSH) US DEPT HEALTH & HUMAN SERVICES
CYC 69
PI WO 9640127 A1 19961219 (199705)* EN 51p A61K031-42
RW: AT BE CH DE DK EA ES FI FR GB GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG
W: AL AM AT AU AZ BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU IS JP KE KG KP KR KZ LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG UZ VN
AU 9661028 A 19961230 (199716) A61K031-42
ADT WO 9640127 A1 WO 1996-US9524 19960607; AU 9661028 A AU 1996-61028 19960607
FDT AU 9661028 A Based on WO 9640127
PRAI US 1995-473960 19950607
REP WO 8805044; WO 8805653; WO 9113619; WO 9505397
IC ICM A61K031-42
ICS A61K031-445
AB WO 9640127 A UPAB: 19970129
Use of a compsn. contg. a carrier and a metal-independent nitroxide or an oxazolidine capable of forming an oxazolidine-1-oxyl or its salts, to protect biological materials from oxidative stress.

The cpd. is pref. of formula (R4)(R5)N(R3) (I), where R3 = O or OH; NR4R5 = heterocyclyl, or R4, R5 = opt. substd. cyclic or heterocyclic gp. such as piperidine, pyrrole, imidazole, oxazole, thiazole, pyrazole, 3-pyrroline, pyrrolidine, pyridine, pyrimidine, purine or deriv.

USE - The compsns. are useful in treating stress due to free radicals formed by an oxidising agent, oxygen-induced degeneration or disease, ionising radiation, carcinogens, chemotherapeutic agents, mutagens, aging, arthritis, reperfusion injury or increased oxygen exposure due to or pulmonary adult distress syndrome or in preventing oxygen-induced lenticular degeneration, cataracts or hyaline membrane disease in infants. The compsns. are also useful in prolonging the shelf life of cells, tissues or organs in vitro (all claimed). They can also be used as protectants against cytotoxicity due to excessive oxidn. in animal or plant cell culture media and in preventing oxidn. of aerobic microorganisms, degradation of labile chemicals, chain elongation during polymer formation, degradation of foods and additives (esp. when preserved by radiation treatment), the effects of paraquat and wt. gain. Admin. is parenteral, intramuscular, subcutaneous, intravenous, intra-articular, transdermal, oral, buccal or in the form of a suppository, an aerosol or drops. 4-**hydroxy**-2,2,6,6-**tetramethylpiperidine**-1-**oxyl** (Ia) is administered orally or intravenously in a daily dosage of 0.1-300 mg/kg or 0.1-200 mg/kg by inhalation. In treatment following exposure to radiation, admin. takes place 30 mins.-24 hrs. after exposure (all claimed).

ADVANTAGE - The nitroxides have low molecular weights, are uncharged and water soluble so easily cross into intracellular areas. Being non-proteins, they are not antigen stimulants, and as they do not contain metals, there are no adverse metal-induced reactions. They are non-toxic and their lipophilicity can be controlled by addn. of organic substits., allowing specific organs or organelles to be targeted.

Dwg.0/11
FS CPI
FA AB; DCN
MC CPI: B07-D05; B07-G; B10-A03; B12-M06; **B14-H01**; B14-S08

=> d all abeq tech l136

L136 ANSWER 1 OF 1 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1999-070179 [06] WPIDS
DNC C1999-020713
TI Treating cancer using nitroxide or prodrug - especially to treat cancers due to genetic defect of cancer regulatory gene or tumour suppressor gene.

DC B02 B03
IN CHERUKURI, M K; DELUCA, A M; MITCHELL, J B; RUSSO, A
PA (USSH) US DEPT HEALTH & HUMAN SERVICES
CYC 83
PI WO 9853835 A1 19981203 (199906)* EN 31p A61K033-00 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM GW HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
AU 9875987 A 19981230 (199918) A61K033-00
EP 986393 A1 20000322 (200019) EN A61K033-00
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
ADT WO 9853835 A1 WO 1998-US10685 19980527; AU 9875987 A AU 1998-75987 19980527; EP 986393 A1 EP 1998-923772 19980527, WO 1998-US10685 19980527
FDT AU 9875987 A Based on WO 9853835; EP 986393 A1 Based on WO 9853835
PRAI US 1997-47724 19970527
IC ICM A61K033-00
ICS A61K031-395; A61K049-00
AB WO 9853835 A UPAB: 19990224
Treatment of cancer comprises administering a nitroxide or a prodrug of it.

The nitroxide or prodrug is alicyclic or heterocyclic and is preferably of formula (I) or (II). R1 = H, OH, OZ, U., =O or Y; Y = a leaving group, which can be converted to H, OH, O. or =O by reaction with a nucleophilic agent; Z = 1-20C aliphatic, monocyclic aromatic, bicyclic aromatic, multicyclic aromatic, 1-20C alicyclic, noncarbon/nonoxygen group, carbohydrate, lipid, nucleic acid or protein; R2-R5 = 1-20C alkyl, 2-20C alkenyl, 2-20C alkynyl or CH2[CR'R'']m-Me; R' = H, 1-20C aliphatic, monocyclic aromatic, bicyclic aromatic or multicyclic aromatic; R'' = H, 1-20C aliphatic, monocyclic aromatic, bicyclic aromatic, multicyclic aromatic, 1-20C alicyclic, noncarbon/nonoxygen group, carbohydrate, lipid, nucleic acid or protein; m = at most 30 and R2 and R3 or R4 and R5 can be connected through at least 1 members comprising carbon or heteroatom; R6-R9 = H, hydroxyl, 1-20C aldehydic, 1-20C keto, primary amino, secondary amino,, tertiary amino, sulphido, disulphido, sulphato, sulphito, sulphonato, sulphinato, sulphenato, sulphamato, metal-containing group, silicone group, halide, 1-20C ester-containing group, carboxyl, phosphato, phosphino, phosphinato, phosphonato, 1-20C alkyl, 2-20C alkenyl, 2-20C alkynyl or CH2-[CR'R'']m-Me; R6-R9 can be attached covalently or noncovalently to a polymer of synthetic or natural origin, where in (I), one of R6 and R7 and one of R8 and R9 can be absent so that a double bond joins the two C atoms to which the remaining R groups are attached; n = 0-20 in (I) and n = 1-20 in (II); X = a heteroatom; R10, R11 = 1-20C aliphatic, monocyclic aromatic, bicyclic aromatic, multicyyclic aromatic, 1-20C aliphatic/aromatic, heteroatomic, 1-20C ether-containing group, 1-20C keto group, 1-20C aldehydic group, carboxamido, cyano, amino, carboxyl, a selenium containing group, sulphato, sulphito, sulphenato, sulphinato or sulphonato; R10, R11 can be connected through an aliphatic and/or aromatic group, or R10 and/or R11 form carbohydrate, lipid, nucleic acid or protein.

USE - The method is used for treating cancers due to a genetic defect of a cancer regulatory gene or a tumour suppressor gene, especially the tumour suppressor gene p53, particularly inherited genetic defects that predispose humans to developing cancer including ataxia telangiectasia, Cowden's disease, Torre's syndrome, Gardner's syndrome, Wiskott-Aldrich syndrome, Peutz-Jeghers syndrome, Bloom's syndrome, Fanconi's syndrome, Wemers syndrome, Chediak-Higashi syndrome, retinoblastoma, Beckwith-Wiedeman syndrome and neuroblastoma. Genetic defects may be induced by a variety of agents that damage DNA e.g. oxidising agents.

Dwg.1/2
FS CPI
FA AB; GI; DCN
MC CPI: B04-B01B; B04-E01; B04-N04; B05-B01A; B05-B01B; B05-B01D; B05-B01E; B05-B01M; B07-D05; B14-H01

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=> d his

     (FILE 'HOME' ENTERED AT 12:12:38 ON 30 JAN 2001)
               SET COST OFF

     FILE 'HCAPLUS' ENTERED AT 12:12:51 ON 30 JAN 2001
               E WO9853835/PN
L1             1 S E3
               E MITCHELL J/AU
L2           379 S E3,E5-E8
               E MITCHELL JAMES/AU
L3           174 S E3,E6-E8
L4             3 S E80
               E RUSSO A/AU
L5           256 S E3-E17
L6            83 S E43
               E CHERUKURI M/AU
L7             4 S E4-E6
L8             2 S E18
               E DELUCA A/AU
L9             6 S E3,E4,E11
L10           13 S E13,E14
               E DE LUCA A/AU
L11           81 S E3,E4,E9,E11
               E LUCA A/AU
L12            9 S E3,E12

     FILE 'REGISTRY' ENTERED AT 12:16:25 ON 30 JAN 2001
L13            1 S 2226-96-2
L14           29 S 2226-96-2/CRN

     FILE 'HCAOLD' ENTERED AT 12:17:49 ON 30 JAN 2001
L15           25 S L13
L16            1 S L14
L17            0 S TEMPOL OR TEMPO OH OR HTEMPO OR HYTEMPO OR HOTEMPO OR TANOL O
L18            2 S L15 AND ?TUMOR?

     FILE 'HCAPLUS' ENTERED AT 12:18:52 ON 30 JAN 2001
L19         1706 S L13 OR L14
L20          694 S TEMPOL OR TEMPO OH OR HTEMPO OR HYTEMPO OR HOTEMPO OR TANOL O
L21            3 S HYDROXY(4W)(TETRAMETHYL OR TETRA METHYL)(1W)(PIPERIDINOOXY)
L22          163 S (TETRAMETHYL OR TETRA METHYL)(S)(HYDROXYPIPERIDIN? OR HYDROXY
L23          319 S (TETRAMETHYL OR TETRA METHYL)(S)(HYDROXYPIPERIDIN? OR HYDROXY
L24          345 S (TETRAMETHYLPIPERIDIN? OR TETRA METHYL PIPERIDIN?)(S)HYDROXY
L25           62 S (TETRAMETHYL OR TETRA METHYL)(S)PIPERIDINOL(S)OXY#
L26           22 S (TETRAMETHYL OR TETRA METHYL)(S)PIPERIDINOL(S)NITROXIDE
L27           66 S HYDROXY(S)(TETRAMETHYL OR TETRA METHYL)(S)PIPERIDIN?(S)OXY#
L28          141 S HYDROXY(S)(TETRAMETHYL OR TETRA METHYL)(S)(PIPERIDINOXY OR PI
L29           32 S HYDROXY(S)(TETRAMETHYL OR TETRA METHYL)(S)PIPERIDINOXY?
L30           22 S HYDROXY(S)TETRAMETHYLPIPERIDINOXY?
L31          702 S L19 NOT L20-L30
L32         2158 S L19-L31
L33           33 S L32 AND L2-L12
L34            1 S L1 AND L33
               E NITROXIDE/CT
               E E5+ALL/CT
L35         5025 S E2+NT/CT
L36           37 S L2-L12 AND L35
L37           40 S L33,L36
L38            1 S L37 AND L1
L39           39 S L37 NOT L38
L40         4495 S L32,L35 AND (PD<=19970527 OR PRD<=19970527 OR AD<=19970527 OR
L41            1 S P53 AND L40
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                E TUMOR SUPPRES/CT
                E E7+ALL/CT
L42         1166 S E1+NT
                E E2+ALL/CT
L43         1771 S E3 (L) TUMOR (L) SUPPRES?
                E GENE/CW
L44         3434 S E3,E12 (L) TUMOR (L) SUPPRES?
L45            1 S L40 AND L42-L44
L46            3 S E3,E12 AND L40
L47           27 S L39 AND L40
L48           12 S L39 NOT L47
L49            2 S L48 AND ?TUMOR?
L50          128 S L40 AND (?NEOPLAS? OR ?TUMOR? OR ?TUMOUR? OR ?CANCER? OR ?CAR
L51           33 S L40 AND (?MUTANT? OR ?MUTAT?)
L52          156 S L50-L51
                E NEOPLAS/CT
L53           24 S E6+NT/CT AND L40
                E TUMOR/CT
L54            0 S E3+NT/CT AND L40
L55            4 S E125+NT/CT AND L40
L56            0 S E124+NT/CT AND L40
                E TUMOR INHIBITOR/CT
                E E4+ALL/CT
L57           17 S E2+NT/CT AND L40
                E NEOPLASM INHIBITOR/CT
L58           45 S E10+NT/CT AND L40
                E E10+ALL/CT
L59          158 S L52,L53,L55,L57,L58
L60           23 S ?MUTAGEN? AND L40
L61          164 S L59,L60
L62           66 S L19 AND L61
L63            2 S L62 AND 4/SC AND ANTIMUTAGEN?/TI
L64            1 S L63 NOT TA98/TI
L65            3 S L62 AND 8/SC AND (RADIOPROTECT? OR RADIOSENSIT?)/TI
L66            1 S L62 AND 62/SC AND PHOTOAG?/TI
L67            9 S L62 AND (1 OR 63)/SC AND (SCAVENG? OR LEUKEMIA OR NEUROBLASTO
L68            7 S L67 NOT (TEPA OR PODOPHYL?)/TI
L69           98 S L61 NOT L62-L68
L70            1 S L69 AND 8/SC AND (RADIATION ONCOLOGY)/TI
L71            1 S L69 AND 14/SC AND NEW DIRECTION/TI
L72            7 S L69 AND 1/SC AND (TMPO OR PRODRUG OR IRRADIATION OR TOXICITY
L73            5 S L72 NOT (TRIAMIDE OR HEPATOCYTE)/TI
L74           19 S L64-L66,L68,L70,L71,L73
L75           23 S L41,L45,L46,L49,L74
L76           27 S L39 AND L40
L77           44 S L75,L76
L78           10 S L39 NOT L77
L79           54 S L77,L78
                E TRANSITION METAL/CT
                E TRANSITION METALS/CT
                E E3+ALL/CT
L80           28 S L40 AND E5,E10,E26,E27,E33,E44,E64,E65,E66,E102-E105,E182,E18
L81            2 S L40 AND E310+NT/CT
L82            5 S L40 AND E311
L83           34 S L40 AND (TRANSITION(S)METAL?)/CW
L84           10 S L40 AND LANTHANID?
                E LANTHANIDE/CT
                E E16+ALL/CT
L85            1 S L40 AND E2+NT/CT
L86            0 S L40 AND E3+NT/CT
                E LANTHANIDES/CT
                E E3+ALL/CT
L87           29 S E2+NT/CT AND L40
                E E2+ALL/CT
L88           11 S L40 AND E7,E84
L89           61 S L80-L88
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L90          13 S L89 AND (1 OR 8 OR 62 OR 63)/SC,SX
L91           2 S L89 AND L61
L92           1 S L89 AND CELL DAMAGE
L93          56 S L79,L91,L92
                SEL HIT RN

     FILE 'REGISTRY' ENTERED AT 13:27:11 ON 30 JAN 2001
L94           5 S E1-E5

     FILE 'HCAPLUS' ENTERED AT 13:27:43 ON 30 JAN 2001
L95        1689 S L13
L96          36 S L95 AND L93
L97          20 S L93 NOT L96

     FILE 'REGISTRY' ENTERED AT 13:28:22 ON 30 JAN 2001
L98           4 S L94 NOT L13

     FILE 'HCAPLUS' ENTERED AT 13:28:58 ON 30 JAN 2001

     FILE 'HCAOLD' ENTERED AT 13:30:40 ON 30 JAN 2001

     FILE 'BIOSIS' ENTERED AT 13:31:07 ON 30 JAN 2001
L99          160 S L13 OR L14
L100         218 S TEMPOL
L101         244 S L99,L100
L102         141 S L101 AND PY<=1997
L103          24 S L102 AND (MITCHELL J? OR RUSSO A? OR CHERUKURI ? OR DELUCA A?
L104          27 S 24?/CC AND L102
L105          10 S L103 AND L104
L106          14 S L103 NOT L105
L107          10 S L103 AND 00520/CC
L108          10 S L103 AND CONFERENCE/DT
L109          14 S L107,L108,L105
L110          10 S L103 NOT L109
L111          17 S L104 NOT L109
L112           3 S L111 AND (CYTOSTATIC OR LEUKEM? OR NEOPLASTIC)/TI
L113          17 S L109,L112

     FILE 'BIOSIS' ENTERED AT 13:37:48 ON 30 JAN 2001

     FILE 'CANCERLIT' ENTERED AT 13:38:18 ON 30 JAN 2001
L114          49 S L101
L115          33 S L114 AND PY<=1997
L116           2 S L115 NOT AB/FA
L117           0 S L115 AND P53
L118          13 S L115 AND G5./CT
L119           2 S L115 AND GE/CT
L120          13 S L118,L119
L121           3 S L115 AND TRANSITION METAL
L122           0 S L115 AND LANTHANID?
                E TRANSITION METAL/CT
                E METAL/CT
                E METALS/CT
L123           3 S E3+NT/CT AND L115
                E LANTHANIDE/CT
                E E4+ALL/CT
L124           0 S E2+NT/CT AND L115
L125          13 S L120,L121

     FILE 'CANCERLIT' ENTERED AT 13:43:48 ON 30 JAN 2001

     FILE 'MEDLINE' ENTERED AT 13:44:18 ON 30 JAN 2001
L126         171 S L101 AND PY<=1997
L127          11 S L126 AND C4./CT
L128           0 S L126 AND OLDMEDLINE/FS
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     FILE 'MEDLINE' ENTERED AT 13:45:54 ON 30 JAN 2001

     FILE 'DRUGLAUNCH' ENTERED AT 13:46:39 ON 30 JAN 2001
                E TEMPOL
L129            2 S E3

     FILE 'WPIDS' ENTERED AT 13:46:54 ON 30 JAN 2001
L130            6 S TEMPOL
                E TEMPOL/DCN
L131            2 S L130 AND CANCER
L132          140 S L20-L30
L133            1 SEA L132 AND (P630 OR P631 OR P632 OR P633)/M0,M1,M2,M3,M4,M5,M
                  6
L134            2 S L132 AND (B14-H01# OR C14-H01# OR B12-G07 OR C12-G07 OR B12-G
L135            3 S L131,L133,L134

     FILE 'WPIDS' ENTERED AT 13:52:53 ON 30 JAN 2001
                E WO9853835/PN
L136            1 S E3
L137            0 S L136 AND L130,L132
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